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THE TOXICOLOGICAL PHARMACOEPIDEMIOLOGY OF SUICIDE

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THE TOXICOLOGICAL PHARMACOEPIDEMIOLOGY OF SUICIDE: POPULATION-BASED STUDIES ON PSYCHOTROPIC-MEDICATION USE IN SWEDEN

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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I have spoke with the tongue of angels

I have held the hand of a devil

It was warm in the night

I was cold as a stone.

—Bono, *"I Still Haven't Found What I'm Looking For"*

To Veronica and my family

In memory of

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ABSTRACT

The act of completed suicide is a complex phenomenon associated with numerous identified individual and combined risk factors. Mental illness and related disorders confer among the highest risks of completed suicide and have consequently been targeted through pharmacological interventions. However, psychotropic medications and their possible effects on completed suicide have proved notoriously difficult to study. Nonetheless, it is of great importance to further investigate these classes of medications and their role in the suicidal process.

The thesis focuses on toxicological verification of psychotropic medication among individuals who have committed suicide or died of other causes in Sweden. We have investigated the potential role of selective serotonin re-uptake inhibitors in the choice of suicide method and demonstrated the level of adherence to and recreational use of the most commonly prescribed non-addictive psychotropic medications in the Swedish population. In yet-to-be-published Study III, we have examined purchasing patterns for psychotropic medications during the year prior to death, as well as the impact of the level of medication adherence upon the risk of completed suicide.

All studies are based on Swedish national registry data from a period of nearly ten years (2005-2014). Full coverage on dispensed prescriptions, results of medico-legal autopsies, causes of death and diagnoses from inpatient care have been used to operationalize investigated exposures and outcomes and facilitate adjustments for confounders in two case-control studies and one methodological study. By the use of the prescription-based algorithm PRE2DUP, purchases of psychotropic medications and calculated lengths of use were compared with forensic-toxicological findings as a measure of adherence. Logistic regression and Cohen's kappa have been the principal statistical methods used. A new measure of continued need of treatment – the dispensation ratio (the ratio of initiated and discontinued prescriptions) – was also developed.

Two of the main findings are that selective serotonin re-uptake inhibitors are associated with violent completed suicide during early treatment among elderly subjects and that presence of other substances (including other medications and illegal drugs) is an important confounder of associations between treatment with selective serotonin re-uptake inhibitors and choice of suicide method. Overall, rates of adherence in the Swedish general population to psychotropic medication, as reflected by therapeutic blood concentrations at forensic autopsy, are good. Biochemically verified incomplete adherence to antipsychotics, as shown in Study III, is associated with a markedly increased risk of completed suicide. The corresponding effect size for antidepressants was shown to be smaller and no longer statistically significant after adjustments for the dispensation ratio.

Forensic-toxicological data are largely conservative biochemically verified measures of the possible impact of psychotropic medication upon the risk of death. By combining such data with national registry data, we have revealed findings of great importance to further suicide prevention and, at the same time, demonstrated a public-health-oriented application of results from medico-legal autopsies, beyond their immediate use in forensic investigations.

LIST OF SCIENTIFIC PAPERS

I. **Jonas Forsman**, Thomas Masterman, Johan Ahlner, Göran Isacsson, Anna Hedström. Selective serotonin re-uptake inhibitors and the risk of violent suicide: a nationwide postmortem study. *Eur J Clin Pharmacol* 2018; doi: 10.1007/s00228-018-2586-2 (e-publication ahead of print)

II. **Jonas Forsman**, Heidi Taipale, Thomas Masterman, Jari Tiihonen, Anti Tanskanen. Comparison of dispensed medications and forensic-toxicological findings to assess pharmacotherapy in the Swedish population 2006 to 2013. *Pharmacoepidemiol Drug Saf* 2018; 27:1112-1122.

III. **Jonas Forsman,** Heidi Taipale, Thomas Masterman, Jari Tiihonen, Anti Tanskanen. Adherence to psychotropic medication in completed suicide in Sweden 2006-2013: a forensic-toxicological matched case-control study. (manuscript submitted for publication).

CONTENTS

LIST OF ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
5HTTLPR	serotonin-transporter-linked polymorphic region
ACTH	adrenocorticotropic hormone
CI	confidence interval
CRH	corticotrophin-releasing hormone
CSF	cerebrospinal fluid
DDD	defined daily doses
FDA	Food and Drug Administration
GC	gas chromatography
ICD	International Classification of Diseases (and Related Health Problems)
LC	liquid chromatography
MS	mass spectrometry
NBFM	National Board of Forensic Medicine
NBHW	National Board of Health and Welfare
OR	odds ratio
PRE2DUP	From Prescription Drug Purchases To Drug Use Periods
RCT	randomized controlled trial
SD	standard deviation
SERT	serotonin transporter
SSRI	selective serotonin re-uptake inhibitor
TOF	time-of-flight
WHO	World Health Organization
;	Semicolon is a break stronger than a comma, but not as final as a full stop.

1 INTRODUCTION

1.1 BACKGROUND

Suicide has throughout history evoked controversy and debate and been a topic of interdisciplinary research, including accounts of historical, philosophical and medical importance. A number of risk factors have over the years been identified for academic and practical clinical purposes to raise awareness and to identify individuals at risk and manage this risk. There exist a variety of suicide prevention strategies possessing different levels of evidence.[1] Pharmacological alternatives for treatment of underlying psychiatric conditions have, furthermore, been suggested as cost-effective interventions in suicide prevention.[2,] However, there has also existed a parallel, long-standing debate about whether psychotropic medications actually do prevent suicide or whether they might even exert a prosuicidal effect.[,3] Although randomized controlled drug trials have been adopted by the medical community since the 1940s, a number of important limitations have made such a study design unacceptable for use in the study of completed suicide.[4] With increased accessibility to electronic health records, including prescription history, real-world data have been possible to use in observational studies. However, despite numerous large, population-based studies investigating antidepressant medications' prosuicidal and antisuicidal properties, results regarding their overall effect on suicide risk have remained inconclusive.[5] Protective effects for completed suicide have, nevertheless, been found regarding the use of lithium and clozapine, as well as in single studies of antidepressants with a prerequisite of continuous drug use.[6,7] There exist, at the same time, discrepancies between studies with regard to how continuous drug use can be operationalized, as well as with regard to complete information on concomitant use of other substances potentially affecting the intended effect of psychotropic medications. This gap of uncertainty can be filled by the use of forensic toxicology, as it offers direct biological measures of substances present in the body. Furthermore, as completed suicide is only possible to study *post factum* the use of postmortem forensics is of particular value.

This thesis is centered on Swedish population-based registry studies that, through the use of forensic-toxicological findings, operationalize biological verification of exposure to psychotropic medications with an aim to further evaluate and develop tools for the application of real-world data in the assessment of the influence of adherence to prescribed medications on completed suicide.

1.2 DEFINITION OF SUICIDE

The term *suicide* stems from the Latin roots *suus* (oneself) and *caedere* (to kill) and was first used by Sir Thomas Browne in 1643.[8] There is a lack of consistency in the literature regarding the use of the term, with intended meanings including *suicidal ideation, suicide attempt*, and the *completed act of suicide*. The intention of this thesis has been to as far as possible investigate *completed suicide*. Thus, if not stated otherwise, the term *suicide* will refer to completed suicide, which is defined by the World Health Organization (WHO) as "*the act of killing oneself deliberately initiated and performed by the person concerned in the full knowledge or expectation of its fatal outcome*". [9]

1.3 A HISTORICAL VIEW OF SUICIDE AND TOXICOLOGY

One of the earliest known written descriptions of depressive illness and suicidal ideation stems from an Egyptian text known as "*Tired of Life*" or the *"Dialogue of Man and his Ba"* by an unknown author from circa 2000 BC.[10] *Ebers Papyrus* (Egypt, circa 1550 BC) is considered to be the first known written account describing naturally occurring toxic substances, such as opium, lead and hemlock. In ancient Greece, following Pythagoras, Plato condemned self-killing and advocated posthumous censure, including burial without honors. Later, the Cynics, as well as both Greek and Roman Stoics, adopted a more liberal stance. Around the time of death of Socrates in 4th century BC, the Greek philosopher and botanist Theophrastus catalogued descriptions of dangerous plants in *De Historia Plantarum*. In the Roman era, *voluntaria mors* – voluntary death – was closely coupled with explicit methods of suicide – *modi moriendi* – to ensure a dignified death.[11] The physician Pedanius Discorides, who served under the emperor Nero, wrote, in the 1st century AD, *De Materia Medica* , which, apart from containing the first formal classification of poisons, is a major historical source on the use of medicine in antiquity.[12]

In Islam, the *Quran* (632 AD), in surah 4:29, explicitly states, *"And do not kill yourselves (nor kill one another)"* [13]; however, suicide in martyrdom – *shahada* – has by some groups been interpreted as a means of carrying out *jihad*. [14] The study and treatment of poisoning is found in the *hadith*, and by the 10th century, the science of toxicology was well established in Islamic countries (as illustrated by, for example, Ibn Wahshiyya's *Book of Poisons* and Avicenna's *Canon of Medicine*).[15] In China, Confucius (who lived from 551 BC to 479 BC) took a positive stance on suicide; however, in later premodern China (i.e., the period between 221 BC and 1800 AD), Confucianism regarded suicide as wrong, in that it violated expectations regarding filial piety.[16] The oldest known writings on forensic medicine stems from 13th century China: in the *Hsi Yuan Lu* ("*Translations to Coroners: the Washing Away*

of Wrongs"), detailed systematic forensic accounts are presented regarding means by which one can distinguish suicides from homicides and accidents, as well as regarding methods by which one can detect "suicide by poisoning". [17]

The development of the Christian doctrine of suicide prohibition followed St. Augustine's publication of his interpretation and extension of the Fifth Commandment, *"Thou shall not kill,"* in 426 AD. This view of suicide as an unrepentable sin was further developed and defended by St. Thomas Aquinas in 1271.[18] In the 16th century, Theophrastus von Hohenheim, or Paracelsus – who is credited as being the "Father of Toxicology" – formulated the maxim "*the dose makes the poison*" and reformed the role of chemistry in medicine.[12] Decriminalization of attempting suicide began across Europe after the French Revolution at the end of the 18th century, and during the 19th century, psychiatry advanced into an autonomous discipline, with independent hospitals and asylums for treatment of mental illness and suicidality. Around the same time, Mathieu Orfila established the modern scientific foundation of forensic toxicology by systematically correlating chemical and biological properties of poisons. In addition, he refined existing analytical methods for toxicological detection, as well as creating several new methods.[12]

During the 20th century, the first right-to-die organizations were formed in the 1930s, with physician-assisted suicide becoming available in Switzerland 1942. During this time, rapid advancements in toxicological detection and automation were seen in the forensic sciences, aided by concurrent broad advancements in analytical biochemistry. In the last hundred years, theoretical mass accuracy of toxicological detection have gone from parts per hundred (10^{-2}) to parts per quadrillion (10^{-15}) – results attainable at a fraction of previous times and costs.[12] Subsequent to the swift availability of Internet in the 21st century, the term *cyberbullicide* was coined in 2007 in reference to individuals taking their own life following harassment over the Internet.[19] In response to live-streamed suicides, major platforms for social media have since developed artificial-intelligence algorithms for automatic screening of suicidality.

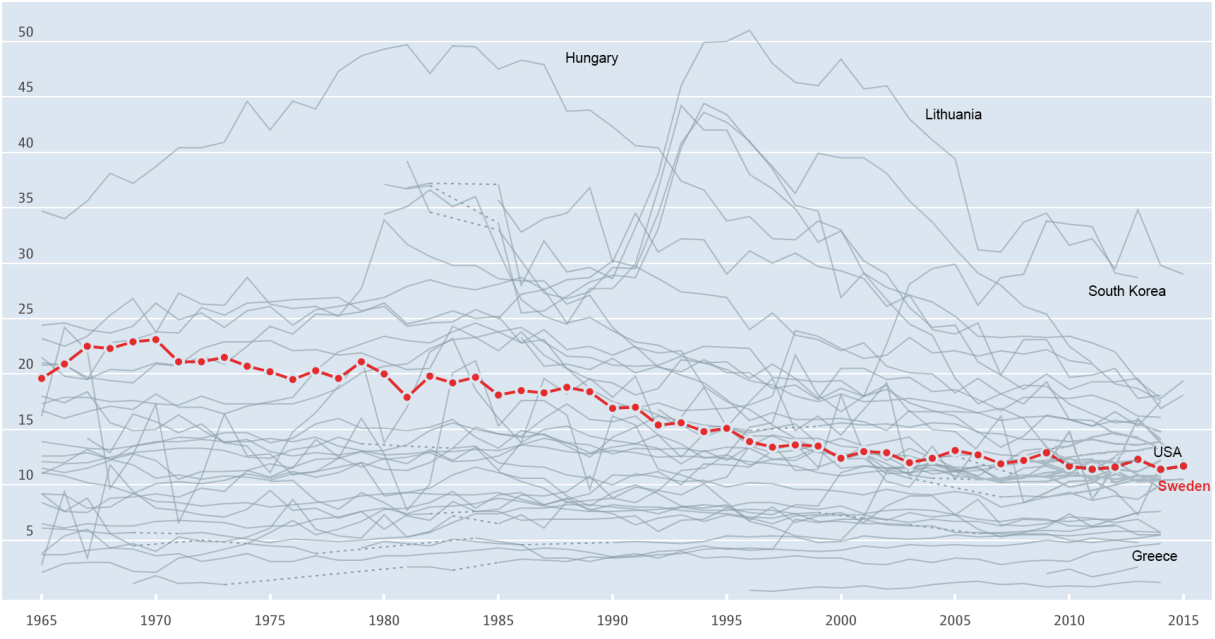
1.4 EPIDEMIOLOGY

In 2015, close to 800 000 people worldwide were estimated to have committed suicide, representing an annual global age-standardized suicide rate of 10.7 suicides per 100 000 inhabitants and accounting for 1.4% of all deaths worldwide.[20] Although reported suicide rates have declined globally since 1990, in 2013 self-harm rose from being the 16th to the 14th leading cause of global years of life lost.[21] Age-wise suicide occurs most frequently among the elderly (70 years or older), and is the second-leading cause of death among people

between the ages of 15 and 29 years. The male-to-female suicide ratio is about 2:1 worldwide but varies between geographical regions, levels of income and age groups. In the Western world, the male-to-female ratio is between 3:1 and 4:1, whereas, in low-income and middle-income countries, it is about 1.5:1.[22] Bangladesh, China, Indonesia, Iraq and Pakistan have been the only countries to report suicide rates in women exceeding those in men.[23] Violent suicide methods are world-wide more common than non-violent means – intoxications – and are predominantly used by men.[24]

During the early 1970s, Sweden reported one of the highest suicide rates in the world, but since then, the country has had a steadily declining rate of registered completed suicides. The reported age-standardized rate of suicide in Sweden for both sexes in 2012 was, according to the WHO Mortality Database, on par with rates in Australia, Chile, Germany, Thailand, Uganda and the United States (age-standardized rate 11.6 to 13.7 suicides per 100 000 inhabitants).[23,25] The reduction in rates of completed suicide has been seen in both sexes and in all but the youngest age group. Among teenagers and younger adults (between the ages of 15 and 24 years), suicide rates plateaued in the 1990s but have during the past decade showed a slight tendency to rise. The Swedish male-to-female-ratio has since 1980 lain between 2.2:1 and 2.7:1.[26] Among same-sex married couples, the risk of suicide has been estimated to be nearly three-fold higher than the risk among different-sex married couples.[27]

Figure 1.1. Age-standardized suicide rates in Sweden compared to in other countries belonging to the Organization for Economic Co-operation and Development (total, per 100 000, 1965-2015). Source: OECD Health Statistics: Health status



1.5 ACKNOWLEDGED RISK FACTORS

Recognized risk factors for completed suicide vary between sexes and across geographical regions and age groups, and have in some studies been identified as potentially consisting of more than 200 non-categorized variables.[28] More broadly, they can be subdivided into acknowledged individual-level and societal-level factors, the main categories of which are described below.

1.5.1 Individual-level risk factors

1.5.1.1 Mental illness

Meta-analyses have over the years investigated overall rates of total and specific psychiatric disorders in people who have committed suicide.[29–33] Being diagnosed with any mental disorder, but also having had a history of psychiatric treatment, confers an increased risk of suicide in comparison to the general population. A diagnosed mental disorder entails an increased risk not only of premature death by suicide, but also of all-cause mortality, which by estimates can be translated a reduction in life expectancy of between 10 and 20 years. The specific psychiatric diagnoses that are currently considered to carry the highest risks of completed suicide are anorexia nervosa, bipolar disorder, borderline personality disorder, major depressive disorder and schizophrenia.[33]

1.5.1.2 Ideation and previous suicide attempt

Expression of suicidal ideation and a previous suicide attempt have been considered to be among the strongest predictors for completed suicide,[34–36] and severe lifetime suicidal ideation is probably the best predictor of completed suicide in the long term [37]. Attempters of violent suicide have been shown to more likely repeat the attempt with a successively higher degree of lethality.[38] Although ideation and a previous suicide attempt can, in part, contribute to the formal diagnosis of an affective disorder,[39–41] they still elevate the risk of completed suicide in other psychiatric conditions, such as schizophrenia.[42,43] Suicidal behavior in itself has been proposed as a separate diagnosis, and it has even been argued that it fulfills the diagnostic criteria for addiction.[44,45]

1.5.1.3 Substance use disorder

In the former Soviet Union and other countries worldwide, total population alcohol consumption has been shown to be strongly positively correlated with trends of national suicide rates.[46,47] At the individual level, repeated cross-sectional studies have shown alcohol intoxication to be present in suicidal behavior and completed suicide.[47,48] Moreover, although

there have been significant discrepancies between publications, the evidence from larger cohort and case-control studies is nonetheless ample, and alcohol use disorder is considered to be an important individual predictor of completed suicide.[49] In substance use disorders other than alcohol use disorder, the literature points to even greater heterogeneity between studies – in part owing to methodological difficulties, such as the issue of possible misclassification of non-intentional lethal overdose. However, the reported risk of completed suicide (expressed as the standardized mortality ratio) in opioid use, intravenous drug use or mixed drug use has repeatedly exceeded that in alcohol use disorder, with standard mortality ratios ranging from 5 to 10.[48,50,51]

1.5.1.4 Personality

Personality characteristics have been suggested to act as stable risk factors that either predispose to psychiatric disorders or in themselves independently confer an increased risk of completed suicide.[52] Among overlapping personality characteristics, "impulsive aggression" and "hopelessness or pessimism" have been put forward as two major dimensions associated with suicidality.[52,53] Although impulsivity does not necessarily include aggressive behavior, the two predispositions have repeatedly been shown to be correlated[54,55] and to confer independently increased risks of highly lethal behavior, including violent suicide attempts and suicide.[52] Moreover, impulsivity is one of the two domains of diagnostic criteria in attention-deficit/hyperactivity disorder.[39,40] In both an earlier meta-analysis and in a more recent Swedish population-based study featuring adjustments for comorbid psychiatric disorders, attention-deficit/hyperactivity disorder been reported to be associated with increased risks of completed suicide (odds ratio [OR]: 5.91 [95% confidence interval {CI}: 2.45–14.27], in the Swedish study).[56,57]

1.5.1.5 Chronic somatic illness

A number of somatic illnesses have been shown to be associated with raised suicide risks, the most commonly associated conditions being chronic obstructive pulmonary disease, coronary heart disease, neurological conditions and several forms of cancer.[29,58–61] These risks have in matched nested control studies from England and Denmark been shown to be elevated among patients in both primary and inpatient care, albeit with higher independence from psychiatric factors among hospitalized patients.[62,63] Investigation of noncancerous pain-related conditions in the National Death Index from the Department of Veterans Affairs Healthcare System (n = 4 863 086), revealed, after adjustment for age, sex and somatic and psychiatric comorbidity, that back pain, migraine and psychogenic pain conferred increase suicide

risks.[64] Diabetes mellitus has, in large prospective (n= 1 234 927) and retrospective matched (n= 1 512 405) cohorts in, respectively, South Korea[65] and Sweden[66], been shown to increase the risk of completed suicide two- to four-fold (OR in males: 2.55 [95% CI: 1.30–5.00], OR in females: 3.64 [95% CI: 1.12–11.86], in the South Korean study; and relative risk for both sexes: 3.36 [95% CI: 2.99–3.79], in the Swedish study). In a sample of consecutively performed autopsies in the catchment area of Helsinki, Finland, Forsman and colleagues showed that suicide victims displayed, on average, elevated HbA1c levels of glycated hemoglobin, consistent with diagnostic criteria for diabetes, yet had lower levels of estimated premortem blood glucose than non-suicidal controls.[67]

1.5.2 Societal-level factors

1.5.2.1 Access to and lethality of means

The proportion of medically identified suicidal acts that result in death varies noticeably across methods of attempted suicide. Incidence rates during the years 1990 to 2003, reported from independent population-based Australian and American studies, ranged from 85% to 97% for the use of firearms to 1% to 7% for the most commonly used methods, medication overdose and laceration with sharp instruments.[68–70] Although the degree of lethality is of paramount importance for the percentage of fatal outcomes, ease of use and accessibility also greatly influence choice of method and the absolute number of deaths.[71–74] There are reports of reduced suicide rates resulting from restriction of means by way of both population-level natural experiments (e.g., transition from toxic to non-toxic household gas and decreased toxicity of motor-vehicle exhaust) and state interventions (e.g., restriction on pesticide sales, restricted access to firearms and market withdrawals of the opioid analgesic dextropropoxyphene). Reported findings have, however, predominantly been of an ecological nature and have almost exclusively involved either common or highly lethal methods.[75–80] Yet, it has been argued that, although the reduction of accessibility of a method decreases its specific use in suicide, the method is readily replaced by other methods, so-called means substitution.[81,82] This claim has been partly called into question, however, by studies reporting relatively low rates (5%–20%) of fatal re-attempts in short-term and long-term follow-up periods, even after highly lethal index events.[35,74,83]

1.5.2.2 Access to health care provision

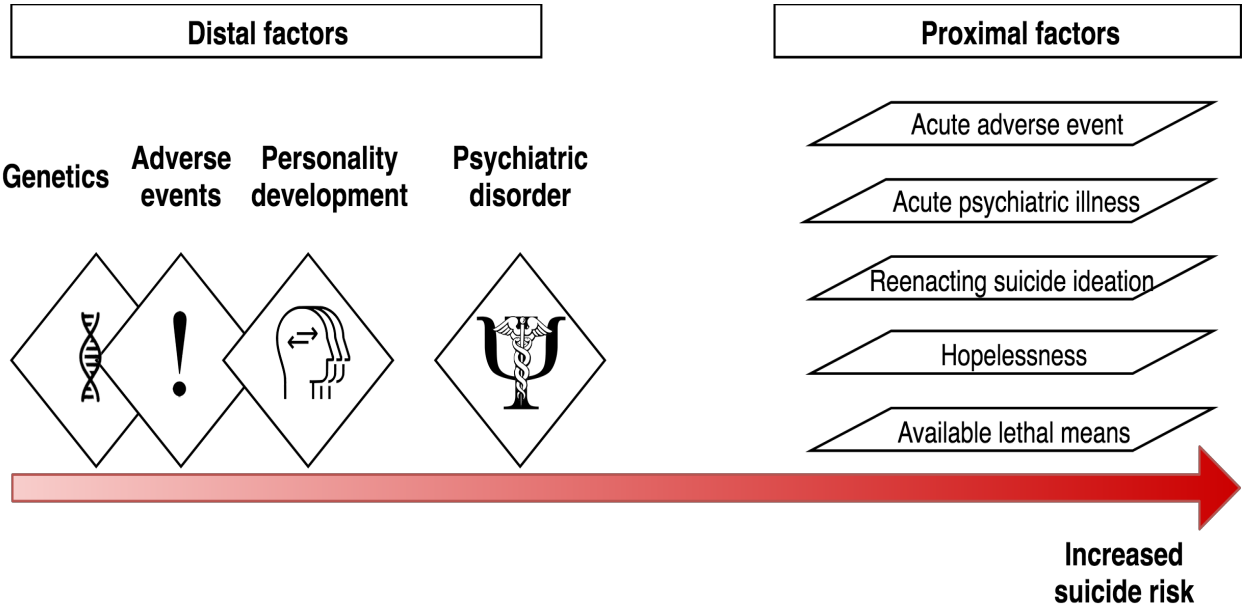
In Finland, studies of the organization of mental health have shown that the availability of outpatient services has protective effects on suicide.[84] Other ecological studies have investigated whether suicide rates might be affected by specific indicators of health care

availability, such as numbers of general practitioners, psychiatrists, physicians, clinical psychologists and social workers. Adjusted for socioeconomic variables, findings from Austria, Japan, Slovenia and the United States have shown an inverse correlation between measures of health care density and suicide rates.[85–88] However, in a later ecological study of 191 countries (which, admittedly, did not adjust for socioeconomic variables or the quality of reported suicide data), the authors concluded that countries with superior psychiatric services have higher suicide rates.[89] With regard to level of care prior to death, Appleby and co-authors found, in a case-control study from the United Kingdom, that suicide victims had had their level of care reduced within the three months prior to death. Reduction of care included reduced appointment frequency, lowered medication dosage, and transfers to a less supervised location.[90]

1.6 THEORETICAL MODELS OF THE SUICIDE PROCESS

Since the beginning of the 20th century, several theories of the suicide process have been developed based on single or combined biological, psychological and social models.[91] In recent years, models proposed by a number of research groups – including the *Stress–Diathesis Model* of Mann and colleagues; the *General Model of Suicidal Behavior* of Maris and colleagues; and *The Integrated Motivational–Volitional Model of Suicidal Behavior* of O'Connor and colleagues – have further distinguished distal, predisposing factors (such as genetic predisposition, adverse childhood experiences and personality traits) from proximal, trigger or volatile factors (such as acute psychiatric illness, sudden adverse events and the availability of lethal methods).[92–94]

Figure 1.6. Examples of distal and proximal risk factors for suicide.



A further elaboration is Dwivedi's scheme of the *Life Span Model of Suicide*, which integrates biological genetic and epigenetic diathetic and proximal stress factors with Joiner's *Interpersonal Theory of Suicide.*[95] Joiner's proposal is that a *capability of suicide* develops throughout life (by repetitive exposure to trauma, violence, self-harm or death) but is counteracted by the innate fear of death or by an insufficient *desire to commit suicide*. This desire is, according to Joiner, made up of, and dependent upon, degrees of *thwarted belongingness* (social alienation or loneliness) and *perceived burdensomeness*. Joiner's theory has been evaluated empirically, with results suggesting robust effects of perceived burdensomeness on suicide *ideation*; however, equally firm evidence regarding completed suicide is still lacking.[96] Dwivedi's model, which is founded on postmortem brain studies, is an attempt to link psychological and neurobiological approaches to suicide research.

1.7 NEUROBIOLOGICAL FINDINGS

1.7.1 The serotonergic system

Historically, evidence of the contribution of low levels of serotonin (5-HT) to suicide risk began to emerge in the 1970s, after low levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) were found in the brainstem and cerebrospinal fluid (CSF) of individuals who had committed suicide.[97,98] Low CSF 5-HIAA levels were later found in depressed subjects who had attempted suicide, subjects who had attempted suicide multiple times and subjects who had attempted suicide using violent methods.[98] Further, findings of low serotonergic functioning have also been replicated in studies of high-lethality suicide attempters and individuals with elevated lifetime aggression [99–103]. Finally, long-term prospective studies have also uncovered an increased risk of completed suicide among individuals with lower 5-HIAA levels in CSF.[104]

There has been a major interest in finding regional differences in serotonergic dysfunction in the brain, and several replicated studies have suggested reduced expression of the 5-HT transporter (SERT) in prefrontal and anterior cingulate cortices – areas involved in decision making and regulation of impulsivity.[105,106] With regard to genes coding for SERT, previously reported positive associations between the less functional *short allele* of the SERT-linked polymorphic region (5-HTTLPR) and both depression and completed suicide have, in later meta-analyses, not been corroborated. Nevertheless, 5-HTTLPR is still thought to play an important role in violent suicidal behavior.[107,108]

Further evidence of low serotonergic function in completed suicide is findings suggesting the activation of compensatory mechanisms resulting from low 5-HT and 5-HIAA levels, such as

up-regulation of the 5-HT_{1A} and 5-HT_{2A} post-synaptic receptors in the brainstem and frontal cortex, respectively.[109] The 5-HT_{2A} receptor is also expressed on blood platelets, where it has been found to be up-regulated among suicide attempters.[110] Age-dependent differences between adults and adolescents in expression and functioning of the serotonergic system after antidepressant exposure – as reflected by differences in density of 5-HT receptors, as well as in the expression of SERT and the function of tryptophan hydroxylase – have been shown in animal models.[111–113] The serotonergic changes appear to occur in a wide range of conditions and have been proposed to characterize violent suicidality per se rather than specific psychiatric disorders.[114–116] Altogether, there is a considerable amount of evidence for the relevance of serotonergic dysfunction as a biochemical trait in depression, aggression, impulsivity and violent behavior, including suicide.[117]

1.7.2 The noradrenergic system

Norepinephrine contributes in the modulation of several behaviors, including stress-response behavior, decision making and regulation of the sympathetic nervous system. Increased levels of norepinephrine are associated with insomnia, anxiety and irritability, while low levels are coupled to lethargy and loss of focus. The relationship between stress, on the one hand, and development of depression, suicidal behavior and suicide, on the other hand, has been convincingly demonstrated.[118] Different forms of distress, including pain, activate the release of norepinephrine in locus coeruleus, and prolonged states seem to induce neural changes in this area, with an increased number of cells [119]. While postmortem studies of suicide victims have found indications of cortical noradrenergic overactivity (e.g., fewer noradrenergic neurons in locus coeruleus and higher binding to both alpha-1 and alpha-2 adrenergic receptors in the prefrontal cortex),[120,121] measurements of norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol in CSF or urine have not conclusively been shown to be markers of completed suicide.[122–124]

1.7.3 The hypothalamic-pituitary-adrenal-axis response system

Among the oldest and most reliable findings in biopsychiatry is the altered activity of the hypothalamic-pituitary-adrenal axis in depression.[125] The main function of the hypothalamic-pituitary-adrenal axis is regulation of the stress hormone cortisol – a fat-soluble steroid that counteracts inflammation and elevates blood glucose. In addition, the hypothalamic-pituitary-adrenal axis interacts in a complex manner with the noradrenergic, serotonergic and dopaminergic systems of the brain.

As a stress response, corticotrophin-releasing hormone (CRH) is released from the hypothalamus and activates the secretion of adrenocorticotropic hormone from the pituitary (ACTH); ACTH acts, in turn, on the adrenal cortex, which produces and releases corticosteroids, including cortisol. Increased blood levels of corticosteroids downregulate further release of CRH and ACTH from the hypothalamus and pituitary, respectively.[126] Elevated levels of cortisol in blood and CSF have been shown to be strongly associated with depression, in particular with treatment-resistant depressive states.[127]Further, depressed individuals have been found, radiologically, to display enlarged pituitary and adrenal glands[128] and, biochemically, to respond abnormally to ACTH and the dexamethasone-suppression test. [i]

In earlier postmortem studies, albeit in the absence of information regarding psychiatric comorbidity, suicide victims have been shown to have enlarged adrenal glands, higher concentrations of CRH in CSF and a lower number of corticotropin-releasing-factor binding sites in various brain regions, compared to non-suicidal controls.[129–131] Although the associations to suicide are convincing, it has been proposed that the findings represent identification of biological substrates of depression and not of suicide per se.

1.7.4 Heredity and genome-wide association studies

Completed suicide is highly heritable and has been shown to be transmitted independently of psychiatric disorders. Findings from aggregated patterns of suicide among biological and non-biological relatives clearly supports the role of genetic influences; however, intermediate behavioral phenotypes, such as impulsive aggression, are likely to moderate these influcences.[132,133]

Genome-wide association studies have the capability to analyze over a million single-nucleotide polymorphisms at once, thus offering an efficient way of in an unbiased fashion exploring large parts of the genome. Whereas several genome-wide association studies have been performed for psychiatric disorders and suicidal behavior, only two peer-reviewed published studies have included suicide completers.[134,135] Gene-expression analyses have identified possible candidate genes linked to function in the prefrontal cortex, to neural-cell death and to inflammatory response. The same findings have not been reported from other

[i] The dexamethasone-suppression test assesses the functions of the adrenal glands by suppression of the secretion of ACTH, which in healthy subjects subsequently decreases blood cortisol levels. Non-suppression upon testing is reflected by normal or elevated levels of cortisol even after administration of dexamethasone.

genome-wide association studies of non-fatal suicidality, but partly overlap with biological pathways identified in studies that have made use of microarray technology to assess large parts of the genome.[134]

1.8 ASSESSMENT OF SUICIDE RISK

1.8.1 Prior contact with health care providers

Although the majority of completed suicides occur in the absence of prior contact with mental health care and without prior warning, in psychological autopsies – which are admittedly plagued by recall bias – a sizable proportion (30%–50%) of suicide victims have been found to have at some time expressed suicidal communication.[136–138] It has further been estimated, in both a comprehensive review and in a large longitudinal study from the years 2000 to 2010, that 45% of suicide victims had interacted with a health care provider at least one month prior to death.[139,140] It has consequently been of great interest to develop readily manageable and accurate tools and routines for suicide-risk assessment even outside the mental health sector.

1.8.2 Theoretical difficulties in suicide-risk assessment

Since the 1960s, several instruments have been established for the assessment of the risk of suicidality, including completed suicide. The instruments have been based upon subjective reports with differing degrees of validated diagnostic predictability (sensitivity[ii] and specificity[iii]) with regard to future suicidal events. Items used in the instruments can generally be categorized as risk factors that are either statistical and trait-dependent (e.g., demographic characteristics, previous suicidality and personality traits) or dynamic and state-dependent (e.g., current stressors and the severity and intensity of ideation and planning). The number of risk factors per test – extracted, by convention from meta-analyses, in order to avoid type I errors[iv] – or even combinations of several tests, will, however, not necessarily increase predictability, in part owing to possible interactions between different factors, to their association with each other and to the extent to which they affect the whole model of prediction.[141,142] Risk-assessment tools have thus been limited with regard to their ability to

[ii] Sensitivity equals the proportion of positive tests among subjects who are affected.

[iii] Specificity equals the proportion of negative tests among subjects who are not affected.

[iv] Type I error refers to a false-positive finding. If the probability of obtaining a result that is the same or more extreme than the actual observed finding is set to 5% (corresponding to a probability value less than 0.05), 5 out of 100 tests will be falsely positive. Meta-analyses decrease the probability of type I errors, since chance findings are not likely to recur in multiple independent studies.

distinguish suicide ideators and attempters from suicide completers – groups that might ultimately be found to represent distinct entities.[143,144]

In a recent comprehensive systematic review by the Swedish Agency for Health Technology Assessment and Assessment of Social Services of the most commonly used suicide-risk-assessment tools (the Beck Hopelessness Scale, the Scale for Suicide Ideation, the Patient Health Questionnaire and the Suicide Intent Scale), no tool proved to display adequate levels of stipulated accuracy (80% sensitivity, 50% specificity) to predict future suicide [145]. However, tools designed to predict rare behaviors, such as suicide, are not only difficult to construct, but also inherently problematic to fully evaluate in the context of their major purpose – immediate and short-term practical management of suicide risk. Even in high-risk populations, rare events require large number of tests in order to be accurately evaluated – a predicament that, inevitably, will generate many false-positive predictions, resulting in unwarranted interventions to prevent the specific outcome. Further, positive prediction of completed suicide will, to a certain degree, be prevented by warranted interventions, thus affecting the "true" accuracy of the test.

Nevertheless, risk-assessment tools are thought to perform no worse than clinical judgment. In addition, they provide valuable checklists and awareness that direct clinical focus to suicide risk and facilitate documentation.[146,147]

1.9 PHARMACOEPIDEMIOLOGY IN SUICIDE RESEARCH

1.9.1 Methodological challenges in suicide research

Pharmacoepidemiology is *"the study of the use and effects, or side effects, of drugs in a large number of people with the purpose of supporting the rational and cost-effective use of drugs in the population and thereby improving health outcomes."* [148] One major concern within the field is the challenges of estimating the impact psychotropic drugs have upon suicide risk, regardless of mechanism. Several classes of prescription drugs have been shown to be influence suicidality, including completed suicide.[149] Owing to methodological challenges, including confounding by indication[v], causality between psychotropic treatment and suicidality has been highly difficult to corroborate or refute. For many other pharmacological substances, prospective randomized controlled trials (RCTs) often serve as the gold standard for evaluating desired treatment outcomes and side effects, since true randomization of a

[v] A confounder by indication is "*a variable that is a risk factor for a disease/outcome among non-exposed persons and is associated with the exposure of interest in the population from which the cases derive."* [278]

large number of participants will distribute known or unknown confounding factors evenly between exposed and non-exposed participants. Prospective RCTs are, however, not feasible to perform for evaluation of completed suicide for ethical, practical and economic reasons. Apart from it being ethically indefensible to conduct trials that, by comparing active treatment to placebo, could potentially lead to unnatural death in somatically healthy individuals, completed suicide is such a rare event that any study would require sizable samples and extensive periods of observation to detect differences between treatment arms upon statistical analysis. Thus, the research field has been forced to use non-experimental observational studies (cohort, case-control, case-crossover, cross-sectional or ecological designs) or to pool data from performed RCTs in registered drug trials – methods with varying degrees of strengths and limitations.

1.9.1.1 Propensity-score matching

The propensity score *is the probability of treatment assignment conditional on observed baseline characteristics.* By matching individuals with identical propensity scores, it is possible to mimic a RCT, since a number of baseline covariates will be evenly distributed between exposed and unexposed individuals. Further, by reducing the propensity score to a single covariate, degrees of freedom and statistical power is spared allowing for smaller study samples without loss of precision, thus making feasible matching, stratification or adjustments even for rare events and subgroups. In theory, the propensity score would suffice as the only variable to match for if the number of constituent covariates were large enough, as this would yield a precise estimate even in the presence of non-identical covariates (such as sex). However, similar to the process of creating suicide-risk-assessment tools, the selection of a set of covariates that accurately estimate the propensity for suicide is challenging. Further, the method has also been criticized as possibly *increasing* imbalance between groups by wrongly assuming complete randomization even when such randomization is not feasible and should be counteracted by alternative statistical measures, such as randomized blocking.[150]

In the review of the literature, the drug classes antidepressants and antipsychotics (including lithium) have been investigated with respect to existing epidemiological findings in support of antisuicidal or prosuicidal effects.

1.9.2 Antidepressants

By virtue of their ability to effectively treat the arguably strongest risk factors for suicidality – depression and suicidal ideation – it has been hypothesized that different classes

of antidepressants might exert protective effects with regard to both completed suicide and nonfatal suicidality.[151,152] However, from their introduction in the early 1960s, imipramine and other tricyclic agents have, in case reports, been linked to onset of aggression and suicidal ideation.[153] Likewise, the first early reports of suicidal ideation and self-destructive behavior associated with selective serotonin re-uptake inhibitors (SSRIs) emerged in the late 1980s and early 1990s.[154–156] Concerns raised over SSRI-induced suicidal behavior and completed suicide were later, in the 1990s and early 2000s, contested by results from meta-analyses of RCTs and propriety clinical data (n ≈ 30 000, 1983–1997) previously submitted to the United States Food and Drug Administration (FDA) and the Medicines Evaluation Board of the Netherlands.[152,157,158] Concurrently, ecological studies were published that reported inverse trends of falling suicide rates and increased sales of SSRIs in the Nordic countries and the United States.[159,160] Subsequent published ecological data from more than 79 other countries revealed, however, discrepancies in this correlation.[88] Nevertheless, most subsequent studies from pooled RCTs and meta-analyses have not found evidence of an overall greater risk of completed suicide associated with antidepressant treatment.[5,161,162] Nor have population-based cohorts (n = 219 088; n = 27 712) and propensity-score-adjusted cohorts (n = 287 543) in the United Kingdom, Holland and Canada revealed significant differences between specific classes of antidepressants in this regard.[163–165] Firm evidence of antidepressants carrying a distinct protective effect for completed suicide has limited support in the literature, but has nonetheless been found for specific medications (sertraline and fluoxetine), as well as in nationwide studies that have taken pharmacoadherence into account.[6,7,166–168]

Standardized suicide rates in clinical trials reported to the FDA since year 2000 have declined by 96% and 63% in patients treated with antidepressants and placebo, respectively, while at the same time, suicide rates in the US have increased. As patients' demographic characteristics have remained the same, the findings may reflect medications' antisuicidal effects. It is, however, more likely that by way of more efficient screening, suicidal patients are to a greater degree, being excluded from clinical trials. [169]

Although the overall support for antidepressants exerting a prosuicidal effect is lacking, discrepancies have emerged with regard to risks of adverse events among the youngest and oldest age strata (younger than 25 years of age and older than 65 years of age, respectively). For instance, in a large (n ≈ 1.2 million) propensity score-matched study of elderly subjects in Ontario, Canada, Juurlink and co-workers found that SSRI treatment increased the risk of violent completed suicide during the first month of treatment (OR: 4.8, 95% CI: 1.9–12.2).[170]

1.9.2.1 Antidepressants in pediatric populations

After reports of possible increased risks of suicidality among pediatric patients treated with the SSRI paroxetine, the FDA released in 2004 their conclusions from a meta-analysis of pooled data (n = 4582) from 24 RCTs of antidepressant use in pediatric patients, as well as a black-box warning regarding antidepressant use among young people that would be expanded in 2007. In the dataset on which the FDA based its conclusions, treatment with SSRIs showed an overall increased risk of suicidality, but not of completed suicide [171]. However, in a broadly matched case-control study (n = 47), Olfson and co-authors have reported an increased risk of completed suicide in a pediatric setting, albeit with a CI whose upper limit was infinity.[172] As a later natural experiment in a cohort of 2.5 million American youths, the issuance of the FDA warning was followed by reduced sales of antidepressants, as well as a paradoxical surge in psychotropic drug poisonings, but no change with regard to completed suicides.[173]

The reported risk of suicidality among children and adolescents has been further investigated for other classes of antidepressants. In neither a large retrospective cohort (n = 36 842), nor a large propensity-score-matched cohort (n=124 097) nor a meta-analysis of RCTs (n=3335) have any clinically meaningful differences between antidepressant medications been uncovered with regard to suicidality.[174–176] Concerning duration of antidepressant exposure in this group, it has repeatedly been shown that the risk of non-fatal suicidal events is increased during the first weeks of antidepressant treatment.[177,178]

1.9.3 Antipsychotics

The risk of completed suicide in schizophrenia has been argued to be mainly related to psychotic and affective symptoms, foregoing suicide attempts and the number of psychiatric admissions, with as many as 2% of patients dying within five years of diagnosis; the lifetime suicide risk has been estimated to be as high as 10%.[179–181] Aside from schizophrenia research indicates that psychotic experiences per se increase the risk of suicide.[182] Prefrontal dysfunction has been suggested as a common biological trait in schizophrenia and lethal suicidality, implying that antipsychotics that improve prefrontal function would also have antisuicidal effects.[183] The second-generation antipsychotic clozapine is unequivocally the medication that mediates the highest prefrontal availability of noradrenaline, dopamine and 5-HT.[184] In both a random-effect meta-analysis (n ≈120 000), a study using a population-based retrospective cohort (n ≈ 5.2 million), nested case-control studies (n = 26 046) and other observational studies, clozapine has shown advantage compared to other psychotropic agents with regard to both decreased risk of completed suicide and all-cause mortality in

schizophrenia.[185–189] Clozapine is, further, one of the few medications that have been evaluated in an RCT with suicidality as an outcome; based on its antisuicidal effects, it is to date the only drug with an FDA-recognized indication of suicide risk (in schizophrenia).[190]

Although, in retrospective review reports and RCTs in bipolar patients, other first-generation and second-generation antipsychotics have been reported to be associated with non-lethal suicidality and akathisia-related suicidal ideation,[191–193] large-population-based studies, as well as a recent meta-analysis including RCTs across several diagnostic categories, have not shown clear associations to completed suicide.[186,187,194] The question of antipsychotics potentially protective effects with regard to all-cause mortality and suicide has been measured in the treatment of schizophrenia.[195–198] In the few studies that have been associated with increased risks of completed suicide during treatment with antipsychotics, the use of first-generation antipsychotics has been predominant, and both inadequate dosage of and non-adherence to neuroleptic treatment have been common.[199,200]

Antipsychotic treatment in schizophrenia has been proposed to follow a U-shaped response curve with regard to completed suicide among patients receiving low-dosage and high-dosage regimens.[196,201–203] With regard to pooled RCT data from the FDA (n = 10 118) or from FDA-defined search methodology (n = 5123), no differences have been shown in rates of attempted or completed suicide between placebo-treated and drug-treated groups for the second-generation antipsychotics olanzapine, risperidone, quetiapine and ziprasidone.[204,205]

1.9.4 Lithium

A large number of studies conducted since the 1970s have confirmed lithium's antisuicidal properties, as well as a protective effect upon all-cause mortality in affective disorders [206]. In a meta-analysis of RCTs from 2013 (48 trials; n = 6674), lithium was found to be superior to placebo, decreasing the number of completed suicides 7.8-fold and death by any cause 2.6-fold.[207] Notwithstanding the large body of evidence concerning lithium's antisuicidal properties, relatively little is known about the substance's mechanism of action. Mood-stabilizing, anti-aggressive and anti-impulsive effects have been put forward as likely mechanisms, although further research is needed for the identification of causal pathways. At any rate, a vital prerequisite for lithium's antisuicidal function is good adherence.[208] In clinical practice, on account of substance's narrow therapeutic window, the concentration of the lithium in serum is regularly monitored, allowing detection of suboptimal adherence. However, for other psychotropic agents – with the exception of clozapine – similar biochemical monitoring is not regularly performed.

1.10 ADHERENCE

Adherence has been defined by WHO as *"the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider"* and has been estimated to be as low as 50% even in developed countries and in psychiatric disorders. Non-adherence is recognized as a significant public health issue as it is related to a number of directly adverse health outcomes, increased costs of medical care, worse prognosis and, ultimately, premature death.[209] [210] For major psychiatric conditions, the dynamic relationship between the degree of disease and level of adherence is of particular importance, since reasoning skills, insight and motivation are all greatly affected by severe mental illness.[211] Non-adherence is, however, considered to depend on number of variables, which, according to WHO, can be schematized as a five-dimensional model consisting of *social and economic factors*, *health-care-related factors*, *condition-related factors*; *therapy-related factors* and *patient-related factors*. The most effective approaches to improving adherence have been shown to target several factors using multiple interventions.[209]

1.10.1 Measuring adherence

Incorrect measurements of adherence lead to difficulties in interpreting results from clinical trials, since they will yield incorrect calculations of treatment efficacy and dose–response relationships. By extension, possible real-world effectiveness becomes even more difficult to estimate.[212] There is, however, no gold standard for measuring medication adherence. Although subjective measurements based on patient diaries, interviews and questionnaires are the most frequently used methods for evaluating medication use, their accuracy is compromised by confirmation bias and recall bias.[213,214] Such methods also run the risk of changing the use of medication and reporting behavior of the participants, by increasing both medication purchases and intake through "white-coat adherence" [215]. This phenomenon may in itself be an important therapeutic intervention, but it gives rise to an artefactual inflation of adherence when it forms the basis for inferences made regarding estimated use of medication in the general population.

Direct objective and biological measures of medication use include sampling of body fluids. Such analyses are also capable of confirming therapeutic drug concentrations, in evaluations of intended efficacy. Nevertheless, as in the case of interviews, anticipated body-fluid sampling is associated with alterations in medication-use behavior. A few studies have implemented unannounced blood or urine sampling, in order to investigate unreported co-

medication and non-adherence to prescribed medications.[213,216–219] Yet, these studies have been conducted in inpatient- or outpatient-care settings and, in most cases, measured in a limited number of selected substances, making them prone to selection bias.

An indirect objective measure that is both less prone to "white-coat-adherence" and cost-effective to implement for a large number of participants is the use of database analysis of consecutive dispensations of prescriptions. This form of measurement assumes, however, that prescription-filling patterns correspond to real-world adherence – that is, that patients regularly take medications as they are generally prescribed. Such methodology is therefore not suited for off-label use and unconventional dosage.

1.10.2 Prescription and dispensing patterns in suicide research

In contrast to distinct periods of exposure described in proprietary data from performed RCTs in meta-analyses, the clear majority of pharmacoepidemiological studies investigating the association between medication and suicidality have used rather simplistic definitions of drug-use periods. Periods of exposure to psychotropic medications have most commonly been modeled either on defined daily doses (DDD)[vi]; on an assumption of one-tablet-per-day use; or on fixed time windows, such as any purchase of medication 30, 90 or 180 days prior to the suicidal event. Regardless of how methods model continuous exposure – for example, by requiring overlapping prescriptions or allowing grace periods between prescriptions – individual prescription-filling behaviors are challenging to fully account for, which has yielded substantial differences between methods.[220] In fields such as cardiology and endocrinology, it has been shown that difficulties in defining continuous exposure run the risk of producing misleading results with regard to protective and harmful effects.[221,222]

While numerous ecological population-based studies have modeled temporal patterns of antidepressant prescriptions and concomitant alterations in rates of completed suicide, the number of studies that at an individual level have tried to construct predictive models linking prescription purchasing patterns to suicidal behavior is limited; what's more, existing studies have focused only on non-lethal events.[223] Adherence to antidepressants, measured simply as a dispensing pattern of more than one purchased prescription, has in nationwide Danish and Finnish cohorts been shown to be associated with decreased probability of completed suicide.[6,7] Likewise, in a study using similarly modeled adherence to prescriptions from

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[vi] "*The DDD is the assumed average maintenance dose per day for a medication used for its main indication in adults*".[148]

from Quebec, Canada, treatment with antipsychotics was shown to lower the risk of suicide in schizophrenia.[224] At the same time, such studies have not been able to answer the following important questions:

- Does initiation of treatment transiently increase the risk of suicide?
- Might periods without prescriptions merely reflect diminished purchasing behavior owing to undertreated severe psychiatric disorder?
- Having filled a prescription, how often do patients actually take their medications?

Thus, even with more sophisticated models of medication use, prescription purchasing patterns still have limitations in their use as a proxy for actual pharmacological treatment and for conceivable direct biological effects of relevance for the suicidal process.

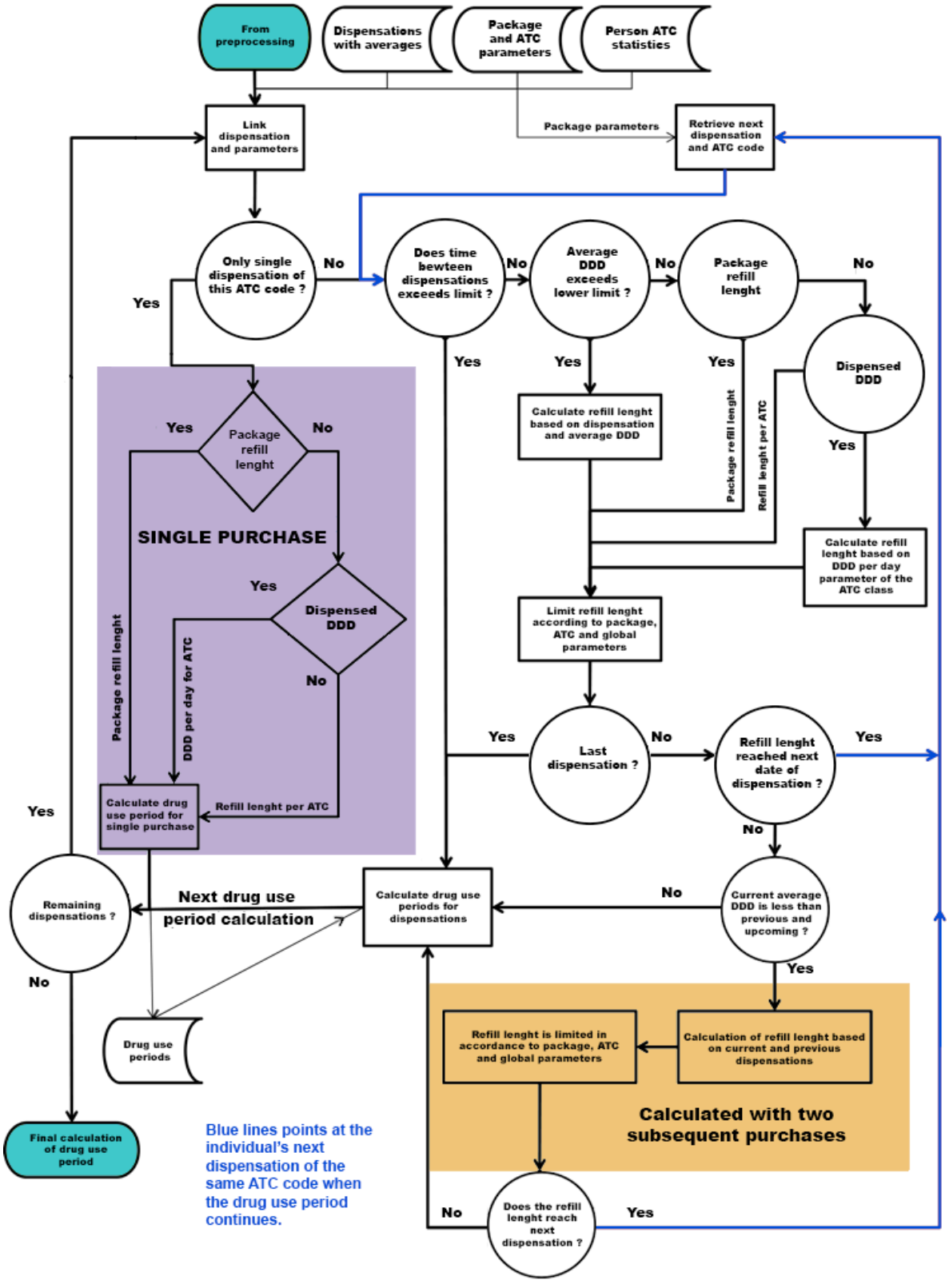
1.10.3 PRE2DUP

Through the use of registry-based prescription data, Tanskanen and co-workers have applied their method, PRE2DUP (an acronym for From Prescription Drug Purchases To Drug Use Periods),[225] in an effort to more precisely estimate continuous drug exposure.[226–228] The validity of PRE2DUP has been evaluated in an interview-based study of person-level agreement between self-reported use of medication and modeled dispensation.[229] In 2006, Tiihonen and co-workers incorporated PRE2DUP in one of the few published studies employing propensity-score adjustments that have reported a protective effect with regard to completed suicide during SSRI treatment.[167]

In contrast to methods (*fixed time windows*, *fixed dosage* and *prescribed dose*) that are static and thus imprecise in their use of parameters to create medication-use periods, PRE2DUP creates *data-driven* models of personal medication-purchasing behaviors by analyzing the individual user's purchasing history. Exposure time periods are constructed and estimates of used doses are calculated based on the purchased amount of DDDs recorded in prescription databases. As alterations in purchasing behavior can be caused by changes in prescribed dosage, stockpiling, shortage at the pharmacy and other factors affecting the personal pattern of medication purchase, PRE2DUP has implemented *sliding averages*[vii] of daily dose. Sliding averages smoothen random variation between dispensations regardless of the cause of purchasing-behavior alterations and individualize an estimated single continuous drug use period.

[vii] *Sliding averages* of daily dose in PRE2DUP are calculated from three subsequent purchases with weighted averages, whereby the last purchase affects the estimate most.

Figure 1.10. Flow chart of core processes in PRE2DUP. Modified from Tanskanen et al., BMC Medical Informatics and Decision Making (2015).



1.11 PHARMACOTOXICOLOGY

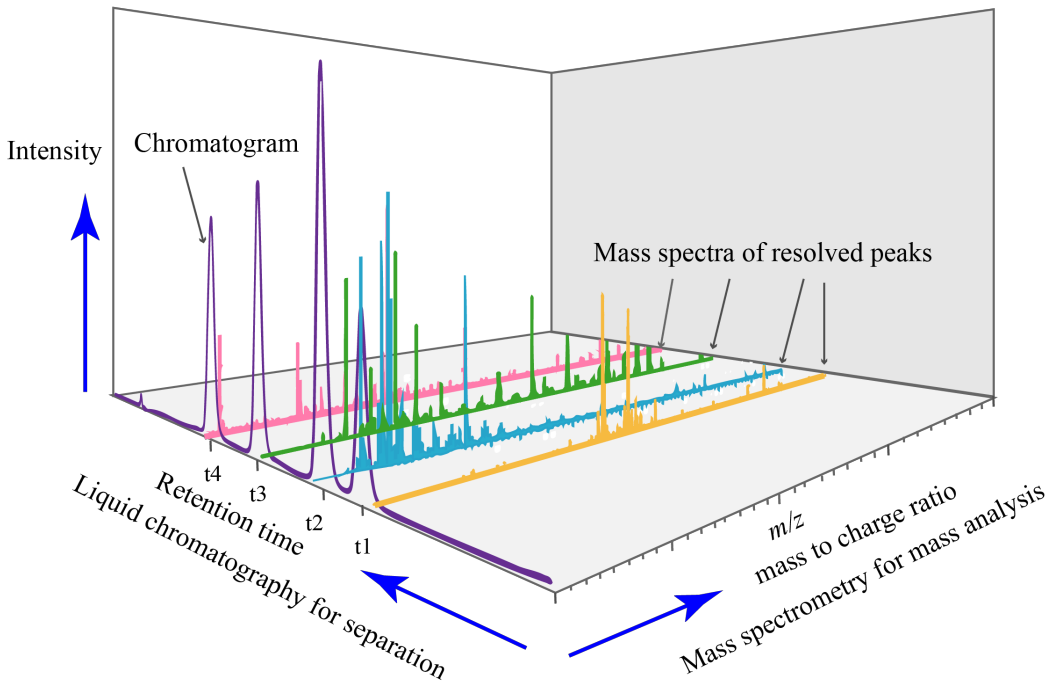
Forensic-toxicological detection of pharmacological substances plays a vital role in modern forensic investigation, given the fact that poisoning is one of the leading external causes of death worldwide. In the United States, both pharmaceutical medications and illicit drugs cause the vast majority of poisoning deaths,[230] whose rates, given the infrequency of toxicological investigation, have presumably been underestimated.[231] Compared to psychological autopsies, medical records and analysis of prescription data, toxicological findings reflect more accurately the presence of biologically active substances and their relevance for the cause of death.

1.11.1 Methods of toxicological detection

For the past few decades, efficient techniques for broad systematic chemical analyses have been developed and used in a variety of fields. In the forensic sciences, techniques using combinations of liquid chromatography (LC), gas chromatography (GC), mass spectrometry (MS) and time-of-flight technology (TOF) have predominated for use in screening for substances, as well as for use in validation and quantification.[232]

Chromatography is a separation technique by which compounds are split into smaller constituents in either liquid or gas form. As a compound passes through a chromatography column, its constituents will react with the column's absorbent lining, and resulting variances in flow rates and retention times will make it possible to differentiate the constituents. By coupling the chromatographer to a spectrometer, the constituents can be further broken down into charged ionized fragments. On account of their unique mass-to-charge ratios, the constituents can then be identified and their concentrations quantified.

Figure 1.11. LC-MS spectrum. Reprinted from Wikipedia.org.



In TOF–MS, charged ions are passed through a vacuum chamber with a certain kinetic energy. Ions with a lower mass-to-charge ratio will travel faster through the chamber, and the time distribution of detection is used for precise measurements of fragment sizes.

The combined techniques of LC–TOF–MS have proved to be a fast and sensitive method for screening a large numbers of known and unknown substances. However, with regard to sensitivity, specificity and dynamic ranges, the method has been surpassed by the much slower combined techniques of GC–MS and LC–MS, making those techniques optimally suited for validation and quantification.[233]

1.11.2 Pharmacotoxicology in forensics

Numerous published reports have presented pharmacotoxicological data and trends with regard to several aspects of completed suicide (e.g., overdose-related findings; differences in age, sex and ethnicity; differences in choice of method; concurrent findings of illegal substances or alcohol; comparison to homicidal deaths; and comparisons of fatal toxicity indices),[234–240] with psychotropic agents generally being the most commonly reported substances found in deaths adjudged to be the result of suicide. However, routines for toxicological testing vary greatly worldwide with regard to case inclusion and selection of assayed substances,[241] with targeted testing being a highly common forensic practice. Thus, collected forensic data have often been prone to various selection biases.

Another difficulty lies in the interpretation of the toxicological results, as levels measured in postmortem samples do not necessarily represent blood concentrations at time of death. Postmortem drug redistribution – the movement of substances between tissues and fluids after death – depends on a number of factors, such as time between death and autopsy, anatomical site, cadaveric changes (blood movement, putrefaction and cell death) and substances' pharmacokinetic properties (acidity, lipophilicity and protein binding).[242] The vast majority of forensically routinely investigated substances have a high postmortem central-to-peripheral drug-concentration ratio – the concentration in the heart and liver divided by the concentration in the femoral vein – which has been correlated with higher postmortem than antemortem blood concentrations, including in the vast majority of instances in which fatal poisoning has been ruled out.[243–245] Further, both absolute postmortem blood concentrations and central-to-peripheral drug concentration ratios have been found to be positively correlated to the length of delay between death and autopsy.[246,247]

Practically, in instances of measurements of blood concentrations of substances that border on fatal toxicity, the general increase in postmortem concentrations may prove to be an

interpretative challenge for the coroner in determining whether death resulted from intoxication or another, natural cause. However, with regard to detection of substances with lower therapeutic ranges or shorter half-lives, increased postmortem concentrations are instead favorable, from a perspective of *sensitivity*, as they result in low rates of false-negative findings.

1.11.3 The pharmaco-toxicologico-epidemiology of suicide

Among studies based upon systematic forensic-toxicological verification, there is still a dearth of analyses that make use of controls.[248–253] Further, owing to obvious practical and legal limitations with regard to antemortem body-fluid sampling, even comprehensive forensic datasets have, by necessity, been cross-sectional and descriptive in nature. Consequently, whereas reliable postmortem toxicology is likely the closest possible representation of actual treatment and biological responses involved in the suicidal process, the stated practical and methodological difficulties have thus far prevented use of toxicological findings for causal inference.

The most common use of *combined* prescription and forensic-toxicological data has been to evaluate causes of death and total number of sales of particular medications regionally, which has allowed calculation of trends and fatal toxicity indices[viii] at the group level. In 1994, Isacsson and co-workers investigated the relationship between diagnoses of depression, prescriptions and concomitant toxicological findings with regard to use of antidepressants by individual suicide victims.[254] This longitudinal approach to forensic toxicology in suicide was again applied by Isacsson and co-workers to: data from Jämtland County for the period 1985 to1995 [252]; SSRI treatment in the Swedish population (1992 to 2000) [255], and on data regarding Swedish youths for the period 2006 to 2010.[256] Recently, a similar methodology was also used in Northern Ireland by Benson and co-workers.[257] However, none of the aforesaid studies has included combined individual toxicological findings and prescription data from non-suicide controls, thus leaving suggested findings of low psychotropic adherence and possible mechanisms in completed suicide open to speculation.

[viii] "*Fatal toxicity index is the absolute number of fatal poisonings caused by a particular medication divided by its consumption figure (number of deaths/DDD)".* [279]

2 AIMS

The overall aim of the thesis has been to investigate possible associations between adherence to treatment with prescribed psychotropic medications and completed suicide in the Swedish population. The ultimate goal has been to provide new knowledge to promote a better understanding of how pharmacotherapy can be improved in groups at risk for completed suicide.

The specific objectives for the included studies are described below.

2.1 STUDY I: SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS AND THE RISK OF VIOLENT SUICIDE

We investigated whether previous findings of an association between the use of antidepressants (selective serotonin re-uptake inhibitors) and method of suicide could be replicated after adjustments for the use of other substances. In addition, we attempted to identify associations related to length of SSRI treatment, age and sex.

2.2 STUDY II: COMPARISON OF DISPENSED MEDICATIONS AND FORENSIC-TOXICOLOGICAL FINDINGS

We investigated real-world pharmacoadherence to treatment with commonly prescribed psychotropic medications and other non-addictive medications in the Swedish population. In addition, we attempted to clarify why factors such as medications' biological half-lives and dosing regimens influenced adherence.

2.3 STUDY III: ADHERENCE TO PSYCHOTROPIC MEDICATION IN COMPLETED SUICIDE

We investigated the extent to which personal-level adherence to treatment with psychotropic medications influences the risk of completed suicide. In addition, we explored differences in patterns of prescription dispensations during the year leading up to death, operationalizing the dispensation ratio – the number of initiated prescriptions divided by the number discontinued prescriptions – as a potential predictor of completed suicide.

3 MATERIAL AND METHODS

3.1 POPULATIONS

The papers included in the thesis are all nationwide population-based studies. The study populations consist of all forensically investigated deaths in Sweden from 2005 to 2013.

Table 3.1: Description of study designs, populations and outcome variables in the included studies.

	Study I	**Study II**	**Study III**
Study population	Suicide victims in Sweden 2005–2012	Swedish population 2006–2013	Swedish population 2006–2013
Study design	Case-control study	Methodological study	Case-control study
Participants	N = 9 553	N = 18 627	N = 15 173
Data sources	National registries ToxBase	National registries ToxBase	National registries ToxBase
Exposure(s)	SSRIs	Non-addictive prescription medications	Adherence Partial adherence Non-adherence (to treatment with psychotropic medications)
Outcome(s)	Violent completed suicide	Agreement between the Prescribed Drug Registry and ToxBase Rate of adherence Rate of recreational use	Completed suicide Violent completed suicide
ICD-10 codes (outcome[s])	X70–X83 Y20–Y33		X70–X83
Covariates	Age Sex Categories of substances Type of SSRI		Age Sex Somatic inpatient care Psychiatric inpatient care Dispensation ratio
Statistical analysis	Logistic regression	Cohen's kappa Shapiro-Wilk normality test Welch's *t* test Mann-Whitney–Wilcoxon test Fisher's exact test	Logistic regression

3.2 DATA SOURCES

3.2.1 Swedish national registries

Since 1947, every Swedish resident has been assigned a 12-digit personal identity number that is based on one's date of birth, which, in research contexts, makes linkage of individual-level data recorded in national registries practically feasible.[258] In the current project, all records were anonymized prior to data analysis.

3.2.1.1 The Swedish Cause of Death Registry

The Swedish Cause of Death Registry is a virtually complete (99.1%) registry on specific causes of death that is coordinated by the National Board of Health and Welfare (NBHW). Since 1952, registered information has been obtained from death certificates collected from local registries. The Swedish Cause of Death Registry includes data on age, sex, date of death and, since 1997, ICD-10 codes regarding underlying and contributing causes of death.[259]

3.2.1.2 The Swedish Prescribed Drug Registry

The Swedish Prescribed Drug Registry, managed by the NBHW since 2005, contains personal-level information on all dispensed prescription in Sweden. It also includes data on generic names of prescribed medications, date of dispensations, Anatomical Therapeutic Chemical Classification System codes, dosages, amounts and DDDs.[260]

3.2.1.3 The Swedish National Inpatient Registry

The Swedish National Inpatient Registry, administrated by the NBHW, possesses virtually complete (99%) coverage of inpatient episodes in Swedish hospitals since 1987. The registry contains information regarding main and secondary diagnoses, as well as their codes according to ICD-9 and ICD-10. A previous validation study by the NBHW has shown that between 85% and 95% of all diagnoses in the registry are correct.[261]

3.2.1.4 The Total Population Registry

The government agency Statistics Sweden maintains the Total Population Registry, which was established in 1968 and contains virtually all data on births and deaths, including sex, parish of birth and birth order.[262]

3.2.2 ToxBase

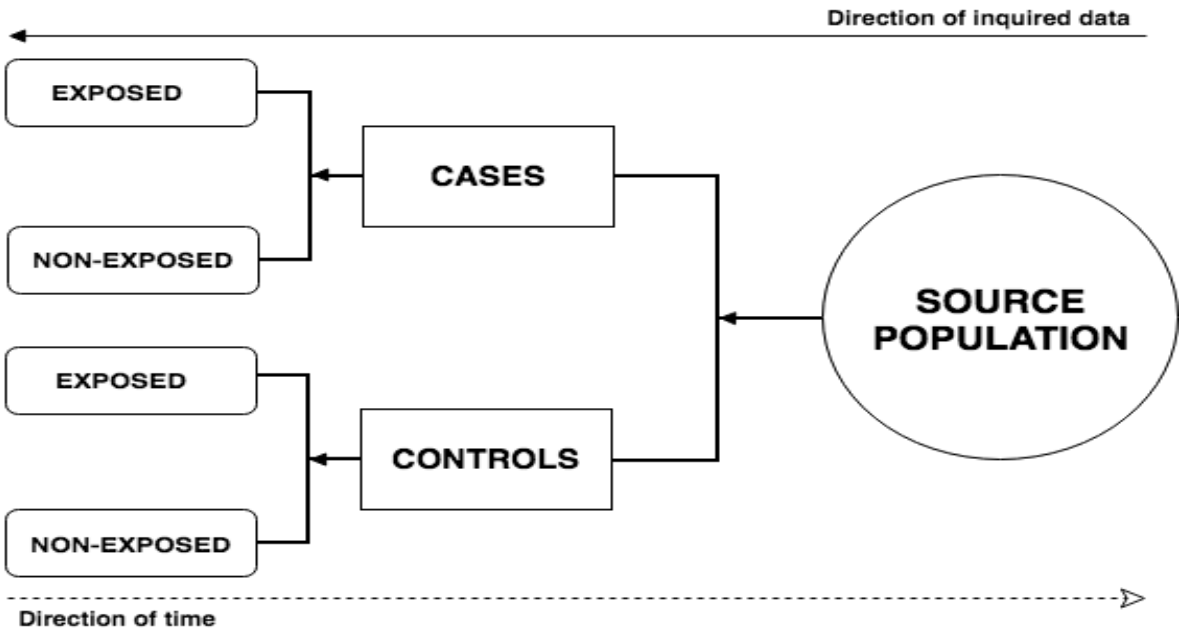
All studies have used forensic-toxicological data retrieved by the Swedish National Board of Forensic Medicine (NBFM). The NBFM conducts all forensic autopsies requested by the police in instances of unnatural or unwitnessed fatalities. Forensic autopsies are virtually always augmented by toxicological analyses performed at the NBFM's department of forensic genetics and forensic toxicology on routinely collected femoral blood, urine and vitreous humor. Toxicological analysis is capable of detecting most legal (and illegal) substances and their metabolites at therapeutic (or recreational) levels, and the results are registered in the NBFM database, ToxBase.[263]

3.3 STUDY DESIGNS

3.3.1 Case-control studies

Studies I and III are observational longitudinal studies based on a case-control design. In a case-control study, two groups from the same source population with a difference in outcome status are followed retrospectively. Once subjects positive for the outcome of interest – *cases* – have been identified, *controls* (negative for the same outcome) are selected. The selection of controls from the source population should be random but can be coupled with matching for variables such as age, sex and geographical region. Collected data of exposure to one or several risk factors is then used to calculate associated risk estimates, expressed as ORs, for the probability of the investigated outcome. The case-control design is well-suited for rare outcomes and thus is usually time- and cost-effective. [264]

Figure 3.3. Study design of a case-control study.



3.3.2 Methodological study

Study II is a methodological study. The focus of a methodological study can be described as *the process used to develop the validity and reliability of instruments and methods to measure constructs used as variables in research.* A methodological study can examine a single method or compare several methods. The purpose is to evaluate the investigated methods to facilitate their further development and systematic application.

In Study II, the PRE2DUP method was applied to data from the Prescribed Drug Registry regarding commonly dispensed non-addictive medications, and results were compared with toxicological results from ToxBase. Thus, results based on PRE2DUP and ToxBase were, in their capacity of alternative measures of ongoing treatment, evaluated in relation to one another.

3.4 OUTCOMES

3.4.1 Study I and Study III: Violent completed suicide

The outcome investigated in Study I was violent suicide, defined as a registered ICD-10 code in the Cause of Death Registry corresponding to a violent suicide method with certain or intentional (X70–X83) or uncertain or unknown intent (Y20–Y33). A sensitivity analysis was also performed with the outcome restricted to certain or intentional suicide.

In Study III, after exclusion of any suicide registered in the Cause of Death Registry as self-poisoning of intentional (ICD-10: X60–X69) or undetermined intent (ICD-10: Y10–Y19) for the purpose of correctly estimating adherence, remaining cases of suicide had been committed using violent methods and coded as certain.

3.4.2 Study II: Agreement, rate of adherence and recreational use

The primary outcome in Study II was agreement (as measured by Cohen's kappa) between, on the one hand, predicted ongoing treatment by PRE2DUP, based on data regarding dispensed prescriptions retrieved from the Prescribed Drug Registry, and, on the other hand, forensic-toxicological findings retrieved from ToxBase. A second outcome in Study II was the rate of adherence to treatment with dispensed medications, measured as the predicted fraction of dispensed prescriptions matching positive toxicology, while a third outcome was the rate of recreational use of the investigated medications, measured as the fraction of dispensed prescriptions without matching positive toxicology.

3.5 EXPOSURE VARIABLES AND COVARIATES

3.5.1 Study I

In Study I, the major investigated exposure was *SSRI treatment*, defined as forensic-toxicological detection registered in ToxBase of any active substance or its metabolite assigned the Anatomical Therapeutic Chemical Classification System code N06AB (fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine). Also investigated was the *duration of SSRI treatment* measured from the date of the first dispensed prescription to the date of death.

All models in Study I were adjusted for the *type of SSRI* and the *number of categories of any detectable substance other than SSRIs* (including other medications and illegal drugs). Stratifications or adjustments were also made for *age* and *sex*.

3.5.2 Study II

In Study II, the major exposure of interest was all *prescription medications routinely screened* by the NBFM, with the exception of addictive medications (benzodiazepines and opioids). Included substances all had to be detectable by accredited analytical methods at a level equal to or below the lowest limit of each medication's recognized therapeutic blood-concentration range.

3.5.3 Study III

The major exposure of interest in Study III was *adherence status* with regard to ongoing treatment with antidepressant and antipsychotic medications as predicted by PRE2DUP, defined as:

Adherence – congruence between predicted occurrence of continuous drug use at the time of death and positive postmortem toxicology for the same medication's active substance or one or its metabolites;

Non-adherence – predicted occurrence of continuous drug use at the time of death in the absence of positive postmortem toxicology for all medications in a particular class;

Partial adherence – a state of simultaneous congruence and incongruence for two or more medications in the same class.

Adjustments were made for *age*, *sex*, *previous inpatient somatic care*, *previous psychiatric inpatient care* and the *dispensation ratio* (the number of initiated prescriptions divided by the number discontinued prescriptions).

3.6 STATISTICAL ANALYSES

3.6.1 Logistic regression

In Study I and Study III, logistic regression was used to calculate risk estimates for the investigated outcome (violent suicide) depending on the various exposures with adjustments for covariates of known and unknown confounders.

In a logistic-regression model, data are analyzed to determine a dichotomous outcome (dependent variable) as a function of one or several independent variables. An independent variable, frequently representing an exposure, can either be discrete or continuous. Knowing the outcome for each point of an independent variable, one can calculate the intercept (the β_0 estimate, reflecting the reference level) and the variable's coefficient (β_n estimates), in order to estimate the odds, or logarithmized probability, that a particular value of the variable will result in the outcome.

$$\log\left(\frac{\pi}{1-\pi}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_m x_m$$

π = *probability*

By exponentiating the β estimates, ORs and corresponding CIs are derived, which commonly are used as an approximation of the relative risk under the rare-disease assumption, that is the assumption of a prevalence of the outcome of less than 10%.

Table 3.2. Example of output of a logistic regression model

Term	β estimate	OR	95% CI	P value
Intercept (β_0)	−1.92	-	-	<0.001
Treatment (β_1)	−0.09	0.92	0.85–1.23	0.405
Age (β_2)	0.18	1.19	0.92–1.31	0.267
Sex (β_3)	0.36	1.43	1.19–1.65	<0.001

3.6.2 Cohen's kappa

In Study II, Cohen's kappa was used to measure agreement between toxicological findings and adherence to the corresponding dispensed medications at the time of death as predicted by the PRE2DUP method.

For categorical data, Cohen's kappa is considered to be a more robust method than agreement calculations based on simple percentages, as it takes into account agreement between raters that could have occurred by chance. According to the formula below, the coefficient κ can be calculated to assume values between 0 (no agreement at all) and 1 (total agreement).

$$\kappa \equiv \frac{p_o - p_e}{1 - p_e} = 1 - \frac{1 - p_o}{1 - p_e},$$

p_0 = relative observed agreement
p_e = hypothetical probability of agreement

		B	
		YES	NO
A	YES	35	55
	NO	5	5

Figure 3.6. Agreement between raters A and B.

Although no standard levels of agreement have been defined, the following arbitrary interpretation of κ has often been used in the literature: *poor* (κ less than 0.20), *fair* (κ between 0.20 and 0.40), *moderate* (κ between 0.41 and 0.60), *good* (κ between 0.61 and 0.80), and *very good* (κ between 0.81 and 1.00).

3.6.3 Tests for equality of means and medians

In Study II, analyses were carried out to using the Shapiro-Wilk test, Welch's *t* test, the Mann-Whitney–Wilcoxon's and Fisher's exact test, in order to investigate differences between true-positive and false-positive users of metoprolol and quetiapine with regard to age, sex, positivity for alcohol, death during any Swedish weekend or holiday, main causes of death, comorbid conditions and type of last medication before death.

Shapiro-Wilk test

The Shapiro-Wilk test is used to the test the normality of the distribution of data. In cases in which data are not normally distributed, the null hypothesis is rejected.

Welch's *t* test

Welch's *t* test, or the unequal variance *t* test, is a parametric test that tests the hypothesis that

two populations have unequal means. Whereas the commonly used Student's *t* test assumes that tested samples are distributed normally with equal variance, Welch's *t* test is used in cases of unequal variance, but with a maintained assumption of normal distribution.

Mann-Whitney–Wilcoxon test

The Mann-Whitney–Wilcoxon test is a non-parametric test that is used when data are not distributed normally; thus, it is commonly regarded as a test of population medians.

Fisher's exact test

Whereas both Welch's *t* test and the Mann-Whitney–Wilcoxon test are used to test for differences between groups in the case of continuous data, the non-parametric Fisher's exact test is used for *categorical data,* especially if there is a small sample size.

4 RESULTS

4.1 STUDY I

4.1.1 Descriptive statistics

From a total of 10 002 forensically investigated incidents of completed suicide, the study population consisted of 9553 subjects. Among men, violent suicide methods were more common than non-violent methods (n = 4585 [67.4%] versus n = 2217 [32.6%]), whereas among women the relationship was the opposite (n = 1251 [45.5%] versus n = 1500 [54.5%]). Mean and median ages were similar after categorization according to exposure to SSRI treatment and suicide method, ranging from 49.4 years of age to 55.7 years of age and from 50 years of age to 57 years of age, respectively. Violent suicide methods were most common in all age groups, but most particularly common in the highest age stratum. The mean number of categories of substances other than SSRIs was higher in subjects who had committed suicide using a non-violent method than in subjects who had used a violent method.

4.1.2 Evaluated risk factors

The crude risk of violent suicide among SSRI-treated individuals was 0.62 (95% CI: 0.56–0.69). In a first model adjusting only for age, all estimates, for both men and women, showed a protective effect of SSRI treatment on the risk of violent suicide. Yet, after further adjustment for sex and categories of other substances, SSRI exposure exerted neither a protective nor a predisposing effect on the risk of violent suicide. In a model stratified by sex and categorized by duration of SSRI treatment an increased risk of committing violent suicide was found for the *shortest duration* of SSRI treatment (0 to 28 days; OR: 3.6 [95% CI: 1.9–6.8]), among both males (OR: 3.6 [95% CI: 1.6–8.1]) and females (OR: 3.9 [95% CI: 1.3–11.9]). The risk was most prominent among subjects above 50 years of age and was, in all groups, attenuated by the length of use. A sensitivity analysis restricted to incidents of certain suicide yielded similar risk estimates.

4.2 STUDY II

4.2.1 Descriptive statistics and screening tests

In the 18 627 included subjects of the study, 63% were younger than 65 years of age, and the mean age was approximately 58 years. Females represented approximately 24% of the sample. The most common main cause of death, at 41%, was disease related to the circulatory system. External causes of morbidity, including vehicle accidents, exposure to electric current or exposure to forces of nature, represented the second most common main cause of death (33%), after exclusion of incidents of certain or uncertain suicide.

Overall, PRE2DUP-modeled drug-use matched toxicology in 46% of instances of presumed prescribed pharmacotherapy. At the group level, this positive predictive value, or predicted adherence rate, was highest for antidepressants, at 71%, and lowest for cardiovascular medications, at 22%. Clozapine was the only analyzed medication that had a predicted adherence rate of 100%.

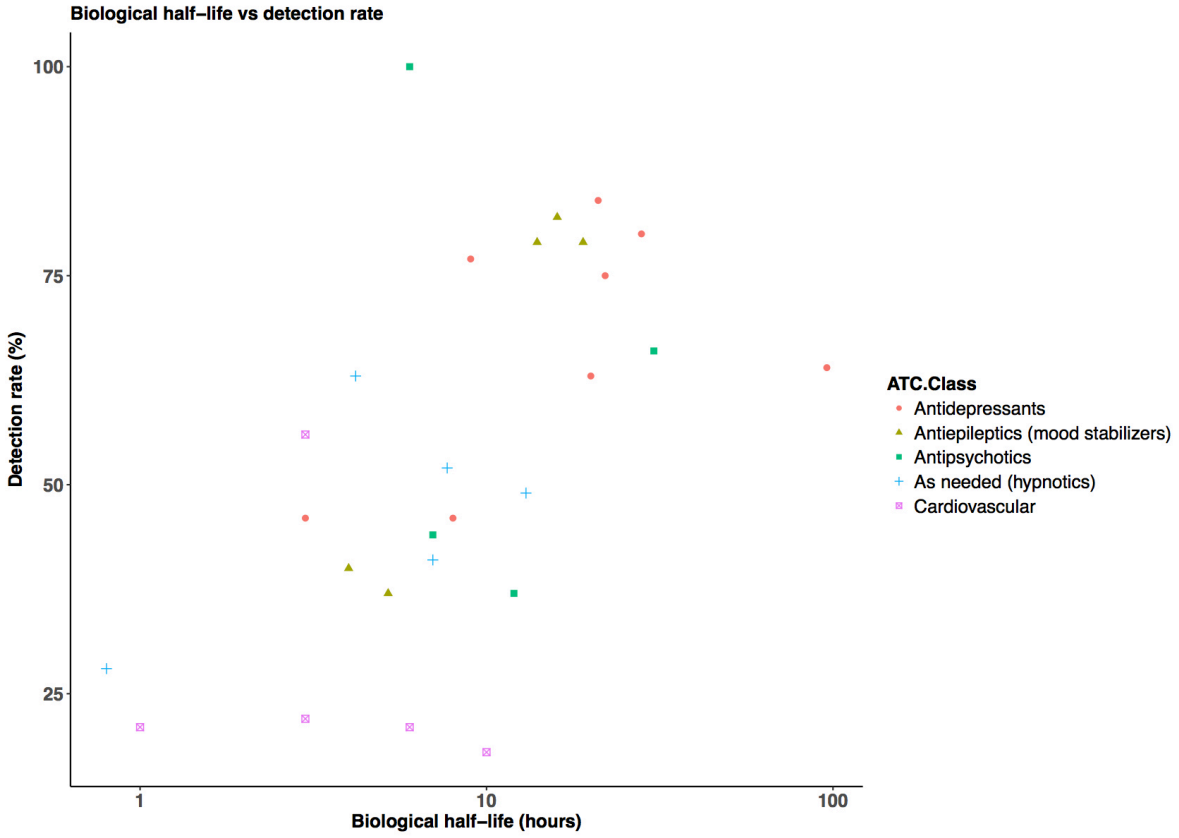
Calculated predicted recreational use, which was generally low, ranged from 0.0% to 1.4% (0.3% overall). The highest levels of recreational use were observed for the sedatives alimemazine (1.4%) and propiomazine (1.1%), both of which are commonly prescribed to be taken as needed.

4.2.2 Inter-rater agreement and detection versus biological half-life

Agreement between toxicology and registry data, measured by Cohen's kappa, was, overall, "moderate" (0.56 [95% CI: 0.55–0.57]). The highest level of agreement was observed for antidepressants (0.74 [95% CI: 0.73–0.76; range: 0.59–0.82], corresponding to "good" agreement), while the lowest level of agreement was observed for cardiovascular medications (0.33 [95% CI: 0.31–0.36; range: 0.29–0.65], corresponding to "fair" agreement). Antiepileptic and antipsychotic medications displayed, at the group level, "good" agreement, at 0.63 (95% CI: 0.61–0.66) and 0.69 (95% CI: 0.65–0.72), respectively (overall range for both groups: 0.47–0.98). "Moderate" agreement (0.53 [95% CI: 0.52–0.55], range 0.39–0.59) was seen for as-needed sedatives.

A positively linear correlation between the detection rate and the biological half-life for each substance indicated greater probability of detection with longer half-lives for most substances. An exception to this trend, however, was found for cardiovascular medications, which displayed an inverse correlation.

Figure 4.1 Plot of half-life versus detection rate. The detection rate is plotted against the biological half-life of each substance. The relationship is positively linear for all medications, excluding cardiovascular medications, for which it is negatively linear. Modified from Forsman et al., Pharmacoepidemiology and Drug Safety 2018; 27:1112-1122.



In post-hoc comparisons of true-positive and false-positive users of metoprolol and quetiapine, a few of the following differences deemed statistically significant were uncovered.

Table 4.1. Comparison of true-positive and false-positive instances of pharmacotherapy for metoprolol and quetiapine.

	Metoprolol True positives	Metoprolol False positives	P value	Quetiapine True positives	Quetiapine False positives	P value
>65 years	**64.8%**	**53.2%**	<0.0001	7.4%	16.2%	0.1729
Female sex	**27.6%**	**21.0%**	0.0075	29.6%	25.0%	0.6821
Heart failure	**21.1%**	**15.7%**	0.0150	3.7%	0.0%	NA
Ischemic heart disease	**30.9%**	**23.9%**	0.0069	3.7%	0.0%	NA
Hypertension	**50.1%**	**35.2%**	<0.0001	7.4%	17.6%	0.1123
Lower strength	**43.6%**	**56.3%**	>0.0001	**33.3%**	**72.1%**	<0.0001
Lower dosing	**75.0%**	**89.2%**	<0.0001	**31.6%**	**65.9%**	0.0019

4.3 STUDY III:

4.3.1 Descriptive statistics

After exclusions and 1:2 matching for age, sex and year of death, the study population consisted of 5294 completed-suicide cases and 9879 non-suicide controls. Among cases 80% were male and 73% under the age of 65 years (mean age: 52 years [SD: 19.9 years]), whereas among controls 82% were male and 72% under the age of 65 years (mean age: 53 years [SD: 19.1]). The most common causes of death among controls were death attributable to external causes and death attributable to diseases of the circulatory system, at 39% and 37%, respectively. Rates of toxicological positivity for ethanol and hypnotics were similar in cases and controls. Opioids and other addictive substances were more common in controls. With regard to previous inpatient care, depression (5.7%), alcohol-related disorders (5.7%) and psychosis (2.6%) were most common among completed-suicide cases, and alcohol-related disorders (23.8%), drug-related disorders (7.6%) and diabetes mellitus most common among non-suicide controls. In comparison with the general population, both cases and controls showed higher prevalence for all diagnoses except pulmonary and cardiovascular conditions.

4.3.2 Differences in prescription dispensations

Among suicide cases, the number of changes per person increased over the year preceding death (all medications, from 0.56 to 1.10; psychotropic medications, from 0.18 to 0.48; and verifiable psychotropic medications, from 0.05 to 0.15), while non-suicide controls showed similar trends (all medications, from 1.03 to 1.49; psychotropic medications, from 0.27 to 0.39; and verifiable psychotropic medications, from 0.05 to 0.08).

With regard to the dispensation ratio, in completed-suicide cases, it decreased, in the year preceding death, for all medications (from 1.15 to 0.96), yet increased for psychotropic medications and verifiable psychotropic medications (from 1.17 to 1.42, and from 1.30 to 1.76, respectively); whereas ratios in non-suicide controls decreased for all types of prescriptions (all medications from 1.15 to 0.66; psychotropic medications from 1.11 to 0.67; and verifiable psychotropic medications from 1.29 to 0.59). A model for linear fitting six months prior to death showed statistically significant slopes of comparable magnitudes for changes in dispensation ratios, but in opposite directions (an increasing trend and a positive slope for completed-suicide cases, and a decreasing trend and a negative slope for non-suicide controls) for all psychotropic medications and toxicologically verifiable psychotropic medications.

Figure 4.1 Comparisons of dispensations ratios of dispensed medications (all medications, psychotropic medications, verifiable psychotropic medications) during the last year prior to death. Ratios exceeding 1.0 represent an increase in prescribed medications and are assumed to be indicators of continued need of treatment.

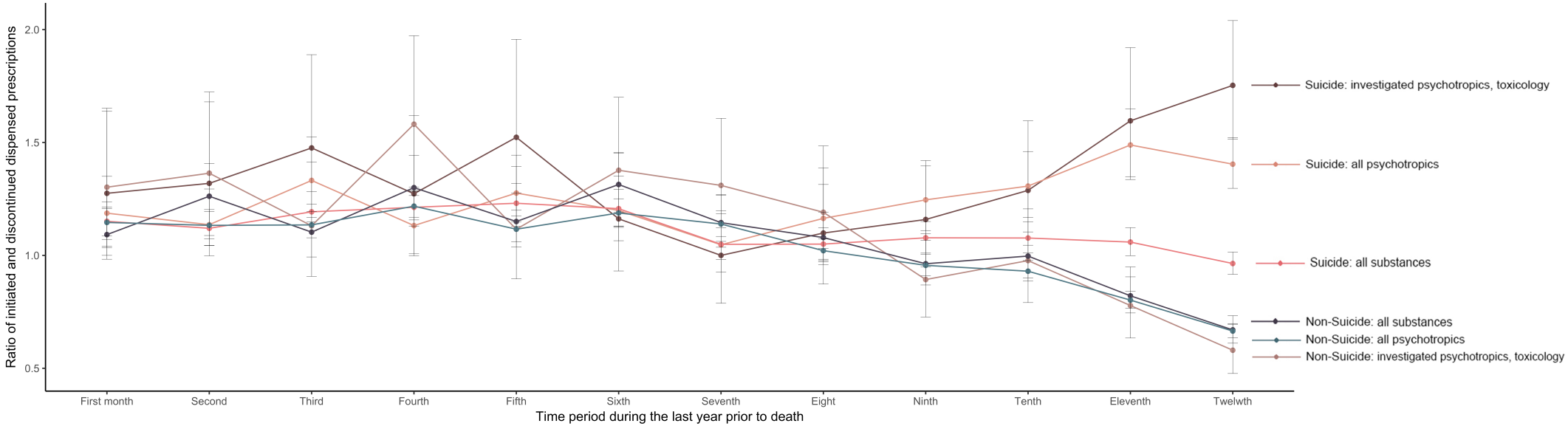
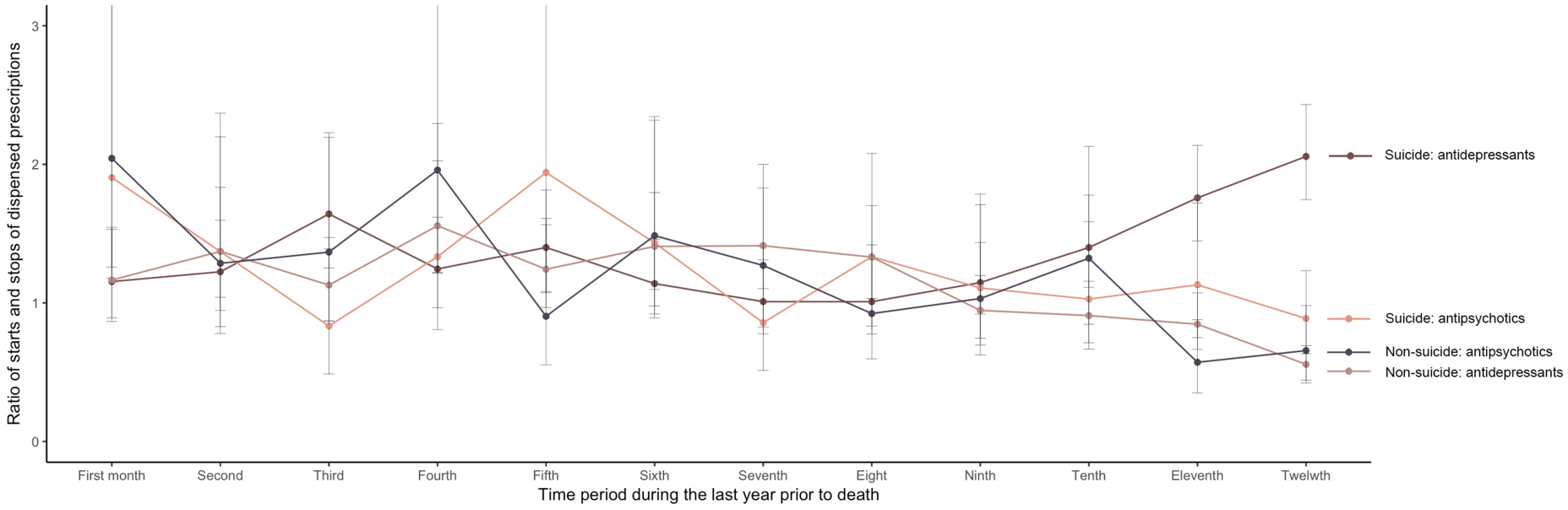


Figure 4.2 Comparisons of dispensations ratios of investigated dispensed medications (antidepressants and antipsychotics) during the last year prior to death. Ratios exceeding 1.0 represent an increase in prescribed medications and are assumed to be indicators of continued need of treatment.



4.3.3 Evaluated risk factors

In a model comparing different degrees of adherence to antipsychotic and antidepressant medications as risk factors for completed suicide, complete adherence was set as reference. Unadjusted risk estimates for non-adherence and partial adherence to *antipsychotics* were OR: 9.51 (95% CI: 2.70–60.30) and OR: 4.59, (95% CI: 1.30–29.16), respectively. After adjustments for previous psychiatric and somatic inpatient care, non-adherence and partial adherence conferred, respectively, the highest and next highest risk estimates (OR: 9.92 [95 % CI: 2.80–63.14] and OR: 4.72 [95% CI: 1.33–30.10]). After a final adjustment for dispensation ratio, risk estimates increased further for both non-adherence (OR: 12.43 [95% CI: 2.06–238.66]) and partial adherence (OR: 6.66 [95% CI: 1.20–128.04]).

Table 4.2. Risk estimates (ORs with 95% CIs) for completed suicide conferred by biochemically verified partial adherence and non-adherence to antipsychotic and antidepressant medications.

		Completed suicides: non-suicide deaths	OR (95% CI)	OR (95% CI) †	OR (95% CI) ‡
Antipsychotics	Adherence	2:18	1 (reference)	1 (reference)	1 (reference)
	Partial adherence	128:251	4.59 (1.30–29.16)	4.72 (1.33–30.10)	6.66 (1.10–128.04)
	Non-adherence	207:196	9.51 (2.70–60.30)	9.92 (2.80–63.14)	12.43 (2.06–238.66)
Antidepressants	Adherence	39:55	1 (reference)	1 (reference)	1 (reference)
	Partial adherence	1186:1064	1.57 (1.04–2.40)	1.43 (0.94–2.20)	1.58 (0.71–3.53)
	Non-adherence	415:363	1.61 (1.05–2.50)	1.59 (1.03–2.49)	1.52 (0.67–3.44)

† adjusted for age, sex, previous psychiatric inpatient care, and previous somatic inpatient care

‡ adjusted for [1] and dispensation ratio during the four months preceding death

For the same model, but comparing degrees of adherence to *antidepressants*, ORs for unadjusted risk estimates for non-adherence and partial adherence were 1.61 (95% CI: 1.05–2.50) and 1.57, (95% CI: 1.04–2.40), respectively. Adjustments for precious psychiatric and somatic inpatient care yielded attenuated risk estimates for suicide, with the risk for non-adherent users being statistically significant (partial adherence: OR: 1.43, 95% CI: 0.94–2.20; non-adherence: OR: 1.59, 95% CI: 1.03–2.49). After a last adjustment for dispensation ratio, the latter risk estimate was no longer significant (OR: 1.52, 95% CI: 0.67–3.44). Analyses of possible interaction effects between sex and adherence status revealed no significant effects for any combination.

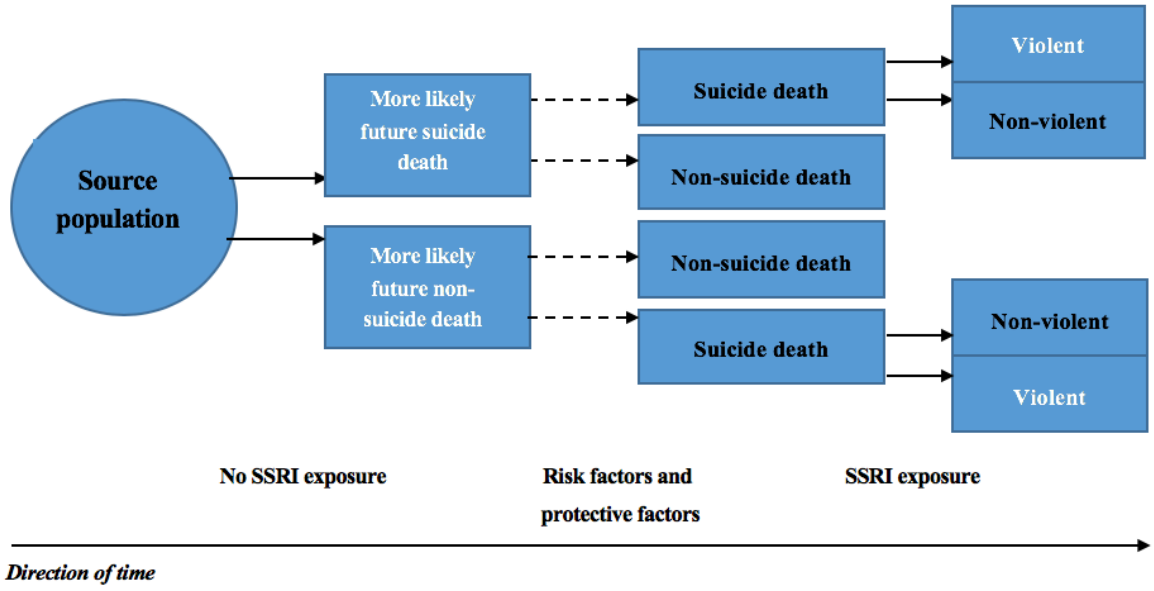
5 DISCUSSION

5.1 STUDY I

In the first study of the thesis, we applied a case-control design to a new theoretical framework of suicide-propensity matching at the group level in order to investigate the previously studied topic of an association between SSRI treatment and violent completed suicide.[265] Study I included personal-level information, including prescription history and postmortem toxicology, for virtually all forensically investigated incidents of completed suicide in Sweden between the years 2005 and 2012.

By employing a completely new theoretical frame work of comparing only incidents of completed suicide, a hypothetical penultimate propensity for this outcome was matched between groups. In theory, this approach removes the need of propensity scoring, allowing more isolated focus on the phenotype of completed suicide. However, it is still possible that earlier exposure to SSRIs could either act as a risk factor or a protective factor, thus affecting the *pre-existing* propensity for completed suicide.

Figure 5.1.2. ***Possible penultimate and ultimate outcomes***

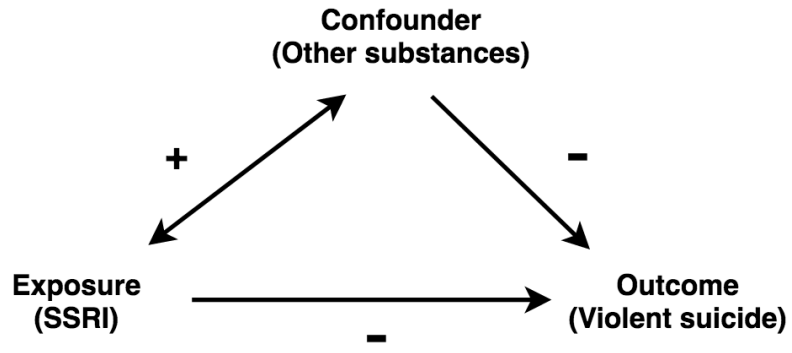


After adjustments for other substances (including other medications and illegal drugs), our results could not replicate earlier findings of SSRIs carrying a protective effect for violent suicide.[265] On the contrary, our findings indicate that shorter duration of treatment with SSRIs, especially among those subjects aged 50 years and older, is an important risk factor for the choice of a violent suicide method. The odds ratio for the risk estimate was 3.6 during the first month of treatment, yet became attenuated with longer treatment durations in both

men and women. Our results are in line with previous findings by Juurlink and co-workers regarding the use of SSRIs and completed suicide by violent methods among elderly in Ontario, Canada, yet contradict the results of Fazel and co-workers, which were based on earlier Swedish data.[170,265] Although adjustments for other substances did not render a result attaining statistical significance for any of the investigated groups of SSRIs, a robust trend of increased point estimates was seen in all models post adjustments. The crude risk of violent suicide among SSRI-treated individuals of 0.62 (95% CI: 0.56–0.69) indicated a *protective* effect of treatment on the risk of violent suicide in the absence of an adjustment for other substances. To our knowledge, this finding is novel and can explain why previous studies have yielded inconsistent results.

Even if the influence of other substances logically can be explained as a confounding variable, because SSRIs are commonly taken together with other substances (as part of psychiatric or somatic polypharmacy or substance abuse), the precise mechanisms underlying early treatment with SSRIs and the outcome of a violent rather than non-violent suicide method is not clear. One possibility is that SSRIs are more readily prescribed to individuals carrying specific risk factors for violent suicide, such as life-time aggression, specific violent behavior, repeated suicide attempts or poorer impulse control, as has been shown in both Finland and Sweden.[38,266,267]

Figure 5.1.1. Other substances acting a as a negative confounder prior to adjustments.



With regard to the timing of the fatal event post dispensation, response to SSRIs in major depression has been shown to depend on several factors, including age and 5-HTTLPR genotype. Both SSRI users carrying the low-functioning 5-HTTLPR genotype and elderly subjects have exhibited latencies to efficiency of therapeutic effect of SSRIs and increased risks of violent suicidality and violent suicide.[108,268,269] Also of interest are polymorphisms within the *ABCB1* gene, which have been linked to violent suicidality and male violent

completed suicide.[270,271] *ABC1B* encodes P-glycoprotein, which is involved in the transport of psychotropic medications over the blood-brain barrier and has been hypothesized to affect treatment response. Altogether, these are important genetic findings that further might offer explanations of our results. A remaining possibility is that violent suicidal behavior is characterized by the continuous need of pharmacological treatment, rather than being caused by it.

5.2 STUDY II

In Study II, we investigated, in a population-based record-linked methodological study, the agreement between continuous drug use as estimated by the PRE2DUP algorithm and findings from forensic toxicology. The study group consisted of forensically investigated incidents of death in Sweden between the years 2006 and 2013, excluding identified cases of completed suicide, as well as cases involving ambulance or hospital care. A similar degree of personal-level information from Swedish registries as was used in Study I was applied in Study II, with, however, the addition of data regarding previous inpatient care.

Agreement between PRE2DUP-modeled medication use and forensic toxicology varied between the investigated medications, ranging from *moderate* to *good*. The highest overall level of agreement and predicted adherence was seen for the use of antidepressants, with the second and third highest agreement levels being seen for the use of antipsychotic and antiepileptic medications, respectively. The lowest level of agreement and predicted adherence was found for cardiovascular medications. The level of recreational use was, overall, very low, but most common among sedatives commonly prescribed to be taken as needed. For all drug classes, with the exception of cardiovascular medications, there was higher probability of toxicological detection for medications with longer half-lives.

Differences of agreement between prescriptions and toxicology uncovered in subsets of quetiapine and metoprolol users confirmed several factors affecting the forensic-toxicological detectability, including low-dosage regimens, lower medication strengths and presumed off-label use. However, regardless of the probable causes underlying lower-than-expected toxicological detection of dispensed medications, our findings still reflect confirmed rates of ongoing treatment with psychotropic medications at *therapeutic levels* in the Swedish population.

Our results of estimated adherence to ongoing treatment are of a similar, yet lower, magnitude than results reported from biochemical monitoring of pharmacoadherence by

means of unannounced sampling: for cardiovascular medications, de Jager and co-workers reported an adherence rate of 32%, compared to 22% in our study; and for antidepressants, Roberson and co-workers reported an adherence rate of 83%, compared to 71% in our study. [216,219]. In comparison to average rates of adherence reported in a review of older studies from 1975 to 1996,[272] as well as rates reported in a large (n = 36 984) interview-based health survey from Canada of psychotropic use in the general population,[273] rates of *non-adherence* appear to reflect relatively high reciprocal rates of continuous use of psychotropic medications in Sweden, especially considering the fact that our study group had been recruited from a forensic setting. In the cited studies, non-adherence to antidepressants was, respectively, 46% and 35%, compared to 29% in our study; non-adherence to antipsychotics was, respectively, 35% and 42%, compared to 42% in our study; and non-adherence to mood stabilizers was 45%, compared to 40% in our study. In a recent study from Austria, only about 25% of the acutely admitted psychiatric inpatients had plasma levels of psychotropic medications within the expected therapeutic range based on dosage.[274]

To the best of our knowledge, no other study has investigated possible recreational use of non-addictive prescription drugs.

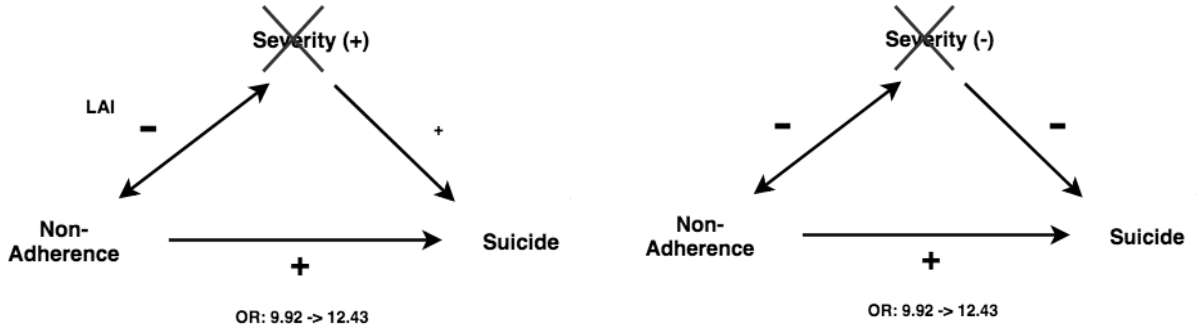
5.3 STUDY III

In Study III, we conducted a matched case-control study investigating different degrees of biochemically verified adherence to antipsychotic and antidepressant medications as explanatory variables with regard to suicide risk, while using non-suicidal deaths as controls. Further, by calculating and comparing the ratio of initiated to discontinued prescriptions for psychotropic medications in cases and controls, we operationalized the ratio as a proxy for continued need of treatment. As in Study I and Study II, we used toxicological results from forensically investigated deaths in Sweden between the years 2006 and 2013, as well as personal-level information obtained from national registries regarding primary and contributing causes of death, prescription history and previous diagnoses from inpatient care.

Our results show that, in comparison with adherent use, both partial adherence and non-adherence to treatment with antidepressant and antipsychotic medications confer increased risks of completed suicide. After adjustment for previous somatic and psychiatric care and continued need of treatment, risk estimates for use of antidepressants were no longer statistically significant, whereas odds ratios for point estimates for use of antipsychotics increased (from 4.72 to 6.66 for partial adherence, and from 9.92 to 12.43 for non-adherence). These findings suggest that a *higher* continued need of treatment was associated

with a greater level of adherence, possibly due to uninterrupted treatment with long-acting injectables among more severely ill patients.

Figure 5.3. Possibilities of an increased association between non-adherence to psychotropic medications and completed suicide after adjustment for dispensation ratio as proxy for continued need of treatment, or severity of suicidality.



In fact, in a post-hoc analysis, it was found that 60% (12/20) of fully adherent individuals had been prescribed long-acting injectables. Corresponding frequencies of prescriptions for long-acting injectables for partially adherent and non-adherent individuals were 12% (46/379) and 11% (45/403), respectively.

The most obvious explanation for the finding that non-adherence and partial adherence conferred increased risks of completed suicide in comparison to complete adherence is that, upon discontinued use, pharmacodynamic antidepressive or antipsychotic effects are no longer present – particularly given the fact that depression and psychosis are robust risk factors for completed suicide. Another possibility is that switching or discontinuation of psychotropic medication may give rise to withdrawal or rebound symptoms, causing distress or even recurrence of previous suicidality.

We have argued that a *dispensation ratio* exceeding 1.0 indicates the continued need of treatment, as the ratio only increases by way of dispensations of newly initiated prescriptions or renewal of non-overlapping historical dispensations – phenomena that occur in instances of insufficient treatment response and increased severity of symptoms and signs, including suicidality. Switching of psychotropic medications, however, will not increase the dispensation ratio, but will instead "dilute" it toward 1.0. Thus, such dilution may lead to underestimation of illness severity, as even switches of medications often represent continued need of treatment. In fact, earlier findings by Hedna and co-workers suggest that switching of antidepressants confers a more than two-fold increased risk of suicide in the elderly. [275]

We have shown that the dispensation ratio may be a useful, fairly proximal and easily measured objective risk factor for suicide, albeit with overall low expected specificity and sensitivity, given the fact that the majority, 55%, of suicide victims lack a psychiatric diagnosis, and that only about the same proportion, 53% in our dataset (data not published), made any purchase of prescription medication during the four months prior to death.[140]

6 METHODOLOGICAL CONSIDERATIONS

6.1 SOURCES OF ERROR

Each scientific study is prone to random and systematic error, which, in turn, affects its reliability. **Random error** represents statistical fluctuations in measurement owing to limitations in the precision of the means of measure. The size of the random error diminishes with the number of observations on account of the self-cancelling of errors above and below the true value. Random error is most commonly expressed as the *standard error* or *CI*. For all studies in the current project, the significance level was set at 0.05. Thus, if the studies were repeated, the true value would be expected to occur in 95% of all repeated tests.

Systematic error, or *bias*, refers to a deviation from reality, in the course of data collection, data analysis, interpretation or publication, that consistently alters the results.[264]

Bias is generally subdivided into the following categories:

Selection bias

Selection bias stems from the procedure of selecting subjects for a study, in which full participation, including follow-up, is influenced as a result of systematic differences either between participants and non-participants of the study (affecting the generalizability), or between exposed and non-exposed subjects in the study (affecting the comparability).

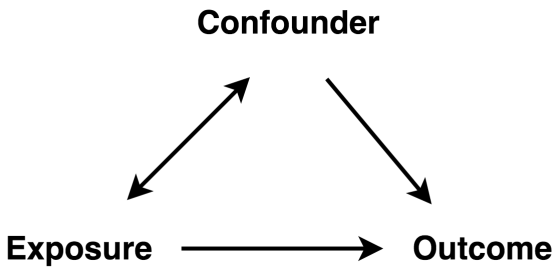
Information bias

Information or misclassification bias results from faults in the way data regarding independent and dependent variables, as well as covariates involved in adjustments, are acquired and classified at registration. Such misclassification leads to incorrect estimates of the association between exposure and outcome. Information bias can be subdivided into *non-differential* or *random misclassification*, which arises when missclassification occurs equally in the study groups, irrespective of investigated exposure and outcome; and *non-random misclassification*, which occurs when misclassification is dependent on exposure or outcome.

Confounding

A confounder is a third variable that offers an alternative explanation for an association between an exposure and an outcome. By not adjusting for the confounder, one distorts the actual strength of the observed association between exposure and outcome. In order for a third variable to be a confounder, it should be independently associated with the outcome and, at the same time, associated with the exposure; in addition, it cannot lie in a casual pathway between the exposure and outcome.

Figure 6.1. Confounding.



Residual confounding refers to unaccounted-for effects of an association, even after measures such as matching, stratification and adjustment have been taken into account. *Confounding by indication* is a particularly troublesome example of confounding in observational studies in which the risk of the outcome of interest resides in the exposed group *prior* to exposure, thus distorting the actual association to the outcome.

6.2 STRENGTHS AND LIMITATIONS

The major strengths of *all* three of the presented studies reside in the use of large comprehensive datasets derived from Swedish national registries and forensic-toxicological results regarding medications and other substances. The national registries possess virtually full coverage and toxicology has been consistently performed in suspected cases of unnatural death, including virtually all reported cases of completed suicide between the years 2005 and 2013. This approach has strongly limited the risk of *selection bias* with regard to the investigated exposures. There still exists, however, an inherent *selection bias* with regard to the use of controls – non-suicide deaths – since forensic toxicology is only performed in instances in which death resulting from the commission of a crime cannot otherwise be ruled out. Nevertheless, although this state of affairs limits the generalizability of the results of Study II and Study III, the results can still be to be regarded as *conservative underestimations*: the population of subjects dying by means other than suicide who have undergone forensic autopsy has, in comparison to the general Swedish population, shown a greater burden of somatic and psychiatric illness, included substance misuse – risk factors for both non-adherence *and* completed suicide.

Another important source of *selection bias* in Study III stems from the exclusion of instances of death by intoxication, which was necessary in order to make possible investigation of adherence status. By way of this exclusion, a third of all incidents of completed suicide were unaccounted for, and, in the resulting sample, younger individuals and women turned out to

be underrepresented. On the other hand, with regard to both the intentionality of death (on account of suicide or accident) and detection of the apparent cause of death, the risk of *misclassification* and *selection bias* is, by way of the exclusion, expected to be substantially reduced. It has been estimated that around half of all unnatural deaths in Sweden are not investigated by means of forensic autopsy. In a study sample from 2008, in 63% of such cases, no cause of death had been registered on the death certificate; in 29% of cases, death was determined to have resulted from an accident, while in the remaining 8% of cases, the cause of death was adjudged to be either self-inflicted or unclear.[276] Previous research has shown that deaths by intoxication are up to 40 times less likely to be categorized as completed suicide, rather than death of undetermined cause, than violent deaths. Understandably, in the absence of a suicide note, the likelihood that deaths by intoxication will be categorized as being of undetermined cause is further increased – indeed, by a factor of 45, as compared to a factor of 8 for violent deaths.[277]

As toxicological findings of pharmacological substances is the closest possible proxy for ongoing pharmacotherapy and biological impact, the possibility of *misclassification bias* of actual influence of substances has, in this project, been minimized. However, a limitation exists with regard to information pertaining to the exact time of death, the time of the last administrated dose and the possibility of off-label use. Further, medications prescribed at lower dosages and substances with shorter half-lives run the risk of not being detected at conventional therapeutic concentrations, leading to underestimation of medication intake. In fact, a positive correlation between biological half-life and detection rate was shown in Study II. In the Study III, substances with half-lives shorter than five hours were excluded, in order to decrease the risk of underestimating adherence to the corresponding medications. Thus, the exclusion is presumed to have, at the same time, increased the sensitivity of positive toxicology.

Any study without sizeable enough randomization and sufficiently low loss to follow-up will run the risk of *residual confounding*. In Study I, by the lack of outpatient clinical data related to the risk of violent completed suicide, the propensity for the outcome was not possible to adjust for, resulting in possible residual *confounding by indication*. Similarly, in Study III, although compared calculated risk estimates were based on dispensations, thus presupposing psychiatric indications for treatment, indicated medical uses for the investigated psychotropic medications are broad. While severity of illness was, in part, accounted for by adjustment for the *dispensation ratio*, residual confounding by indication – specifically, the effect of illness severity on both adherence and suicide risk – still cannot be ruled out.

Through the use of data from a large number of suicides and non-suicide deaths, good statistical power was achieved – a fact reflected by the narrow calculated 95% CIs in all studies. An exception, however, are the analyses of adherence status with regard to *antipsychotics* in Study III, owing to the low number of wholly adherent users in our dataset. There, the 95% CIs widen with each new addition of covariates to the logistic-regression model. The final results, however, are still statistically significant, and the trend across analyses is robust. Nonetheless, a possible improvement could be to use propensity-score matching. Although consensus is lacking with regard to how propensity scoring should be defined and quantified, the method still offers an efficient option for handling a large number of covariates that conserves degrees of freedom and statistical power. Using this method, smaller sample sizes can be used without loss of precision, making feasible matching, stratification and adjustments feasible, even for subgroups and in the case of rare events.

7 ETHICAL CONSIDERATIONS

Suicide has historically been, and at present remains, a taboo subject that often causes discomfort, fear and sadness. Consequently, it is of great importance that consideration is given to relatives, and to the memory and reputation of the deceased. In order to strike an optimal balance between ethical considerations and societal benefits within the framework of this doctoral project, we have followed established laws and ethical research principles, as well as our personal convictions.

The current project makes use of information pertaining to deceased subjects retrieved from existing forensic databases and national registries, making unnecessary considerations that are otherwise relevant in the case of living individuals, such as the risk of physical injury and informed consent. In fact, from the viewpoint of the Regional Ethics Board in Stockholm, which approved the current project (registration number 2013/1411-31/5), our registry-based research data on deceased subjects are *not* covered by the Swedish Ethical Review Act.

The raw data obtained from the NBHW was doubly anonymized – through the removal of personal identity numbers prior to analysis and presentation of results at the group level after analysis – making identification of particular individuals impossible. Sensitive information, such as code keys, have been handled conscientiously and stored in a safe place. Through these procedures, it has been ensured that no single individual or relative would be harmed by the exposure of private information.

Attempts to contact relatives of the deceased for their consent to enquire about the attitudes of the deceased have, for practical and ethical reasons, not been carried out. First, it would have been practically difficult to identify relatives to the more than 40 000 subjects included in the databases and registries; and, second, contacting relatives seemed ethically questionable, since it would run the risk of evoking unpleasant memories. Although use of a smaller sample might theoretically have made feasible contact with relatives, it would have violated another important ethical research principle, namely the imperative of performing adequately powered studies that, on account of the robustness of their results, could benefit society.

Finally, despite efforts to minimize potential damage, the research area is of such a nature that discomfort cannot be ruled out completely. However, the current project's potential moral, practical and socials benefits are believed to outweigh possible disadvantages.

8 CONCLUSIONS

The association between suicide and use of psychotropic medications is neither novel, nor surprising, since the majority of people who take their lives suffer from psychiatric disorders. The use of pharmacological treatment and other psychiatric and social interventions is widespread, yet the assessment of suicide risk is complex. Neurobiological postmortem findings in suicide overlap with current models of psychotropic functioning, yet the specific mechanisms underlying suicide are still largely unknown. With the exception of clozapine and lithium, evidence for psychotropic medications conferring antisuicidal or prosuicidal effects remains inconclusive. Previous scholarship has not been able to explain whether initiation of treatment transiently increases the risk of suicide; whether the purchasing behavior of subjects without dispensed prescriptions in part reflects undertreated depression; or how often patients, having filled a prescription, actually take their medications.

In the papers in this thesis, by way of postmortem toxicological verification of exposure to prescribed psychotropic medications, we have investigated the association between SSRI treatment and violent suicide; adherence to common non-addictive psychotropics in the general population; differences in psychotropic purchasing behavior; and the extent to which incomplete adherence to treatment with psychotropics affects the risk of completed suicide.

Based on the results of this thesis, the following **conclusions** are drawn:

1. Treatment with SSRIs seems to influence the choice of suicide method during early treatment, particularly among elderly subjects. This effect is confounded by the use of other substances (including other medications and illegal drugs). A likely reason for this association is latency to onset of antidepressive effect, but it is still unclear how such latency specifically influences the ultimate method of suicide.
2. Adherence to psychotropics at therapeutic levels in the general population is higher than what would be expected from previous research and highest among subjects treated with antidepressants. Postmortem toxicological detectability of medications is influenced by a number of factors, including unconventional dosing and biological half-lives.
3. Adherent users of antipsychotics carry a lower risk for completed suicide compared to partially and non-adherent users. Results regarding suicide risks conferred by incomplete adherence to antidepressants remain inconclusive. The ratio of initiated to discontinued dispensations of psychotropic medications increases markedly among suicide victims compared to non-suicide deaths during the months prior to death, indicating a possible operationalizable measure of continued need of treatment and severity of suicidality.

9 IMPLICATIONS FOR THE FUTURE

9.1 CLINICAL IMPLICATIONS

Our findings indicate that users of SSRIs during early treatment run an increased risk of choosing a violent suicide method, and thereby an increased risk of suicide completion. However, we do not yet know whether this risk is part of an ongoing suicidal process, including previous and escalating attempts, or a newly initiated behavior. Given that SSRI treatment is an important therapeutic option for a rather wide range of psychiatric disorders, ongoing treatment should not be discontinued, nor initiation of treatment delayed, based on our findings.

Although our results indicate a higher than expected level of adherence to psychotropic medications in the general population, a large rate of non-adherence was nonetheless uncovered, not least among users of antipsychotics. Given that we have shown that partial and complete non-adherence increase suicide risk in this group, clinical efforts aimed at improving adherence – such as patient education, increased frequency of clinical visits, measurements of blood concentrations of prescribed antipsychotics and social support – should also prevent suicide.

Furthermore, our results indicate that violent suicidality may be counteracted by adherent antipsychotic use, although its general antisuicidal effect is yet to be investigated. Nevertheless, when other forms of treatment for suicidality have failed, antipsychotics should be tried, not least since adherence to antipsychotics may be ensured through the use of long-acting injectables.

Finally, changes in dispensations of psychotropic medications that are indicative of switching and increased polypharmacy could possibly be implemented as a warning sign, in response to which the threshold for inpatient care might be lowered to prevent suicidal behavior.

9.2 FUTURE PERSPECTIVES

In the course of this doctoral project, several questions have emerged that merit further research.

A general antisuicidal effect of antipsychotics?

In the light of our findings, further research is called for to investigate the possible general antisuicidal effects of antipsychotic medications, especially with regard to treatment with long-acting injectables. In addition, it is of importance to assess how regimes combining antidepressant and antipsychotic medications affect suicide risk.

Pharmacogenomics and adherence

Pharmacogenetic testing may serve as a tool to provide information about the likelihood of adverse responses to a medication that could jeopardize adherence, increasing the risk of suicide.

Hair analyses in toxicological pharmacoepidemiology

Postmortem blood sampling provides detailed information concerning substance use, but forensic sampling is most often restricted to single instances of cross-sectional sampling. Through the use of toxicological hair analyses, several time periods of substance use and non-use may be uncovered across a span of time, allowing longitudinal assessments and speculations concerning causality. In addition, through the use of this approach, exclusion of cases of non-violent suicide resulting from intoxication can be avoided.

Extended use of the *dispensation ratio*

The dispensation ratio has thus far only been used to analyze violent completed suicide. The method is, however, suited for a range of outcomes and could possibly be integrated into automated prospective studies of pharmacovigilance.

Other sources of outpatient data in suicide research

In an attempt to distinguish violent behavior as a side effect of psychotropic treatment from confounding by indication, real-world historical outpatient information concerning aggression, violence and type of suicidality prior to initiated psychotropic therapy could be studied. Registries of interest in this regard include *the Stockholm County Council Outpatient Registry*, *the Criminal Records Registry* and *the Records of Suspected Offenders Registry*.

10 POPULÄRVETENSKAPLIG SVENSK SAMMANFATTNING

Det fullbordade självmordet är ett komplext fenomen som har kopplats till ett stort antal riskfaktorer. Psykisk sjukdom medför en av de högsta riskerna för självmord och är mål för läkemedelsbehandling i bland annat suicidpreventivt syfte. Läkemedels självmordsskyddande effekt har emellertid varit svår att utvärdera och ytterligare kunskap om behandlingsformens möjliga roll i suicidprocessen är av stor vikt.

Avhandlingens syfte har varit att fokusera på biokemisk bekräftelse av läkemedelsbehandling bland individer i Sverige som avlidit i självmord eller av andra orsaker. Vi har undersökt antidepressiva läkemedels (SSRI, selektiva serotoninåterupptagningshämmare) roll vid val av självmordsmetod samt åskådliggjort graden av följsamhet till psykofarmaka i den svenska befolkningen. I en ännu opublicerad studie har vi därtill undersökt mönster av receptuttag före död samt till vilken grad läkemedelsföljsamhet påverkar risken för fullbordat självmord.

Studierna i avhandlingen har baserats på svenska registerdata från nära ett decennium (2005-2014) med heltäckande information rörande uthämtade läkemedelsrecept, rättsmedicinska obduktionsresultat och registrerade diagnoser i samband med sjukhusvistelser. Läkemedelsföljsamhet har värderats genom jämförelse mellan uthämtade läkemedelsrecept och fynd av läkemedel i blod vid dödstillfället. Genom att jämföra andelen påbörjade och avslutade läkemedelsbehandlingar har vi därtill utvecklat ett mått på sjukdomsgrad.

Våra fynd pekar på att SSRI-behandling kan kopplas till val av våldsam självmordsmetod i tidig behandling hos äldre. Vidare har vi klargjort att andra substanser (läkemedel och illegala preparat) är en viktig påverkande faktor vid utvärdering av SSRI-läkemedels inverkan vid val av självmordsmetod. Följsamhet till icke beroendeframkallande psykofarmaka i den svenska befolkningen har vi visat vara överlag god. Slutligen ger våra resultat bevis på att bristande följsamhet till psykosdämpande läkemedel är kopplad till en tydlig förhöjd risk för fullbordat självmord.

Sammanfattningsvis, genom att kombinera rättsmedicinska analyser med svenska nationella registerdata, har vi visat på läkemedels möjliga inverkan vid självmord. Fynden är av värde för framtida självmordsförebyggande arbete och belyser att resultat från rättsmedicinska obduktioner även kan komma till nytta för en bredare allmänhet.

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12 REFERENCES

1. Zalsman, G. *et al.* Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry* 3, 646–659 (2016).

2. Sharma, T., Guski, L. S., Freund, N. & Gøtzsche, P. C. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ* 352, (2016).

3. Ludwig, J., Marcotte, D. E. & Norberg, K. Anti-depressants and suicide. *J. Health Econ.* 28, 659–676 (2009).

4. Bothwell, L. E. & Podolsky, S. H. The emergence of the randomized, controlled trial. *N. Engl. J. Med.* 375, 501–504 (2016).

5. Pompili, M. *et al.* Antidepressants and suicide risk: a comprehensive overview. *Pharmaceuticals* 3, 2861–2883 (2010).

6. Haukka, J. *et al.* Antidepressant use and mortality in Finland: a register-linkage study from a nationwide cohort. *Eur. J. Clin. Pharmacol.* 65, 715–20 (2009).

7. Sondergard, L., Kvist, K., Andersen, P. K. & Kessing, L. V. Do antidepressants prevent suicide? *Int. Clin. Psychopharmacol.* 21, 211–218 (2006).

8. Brian, B. & Shepherd, D. A necessary neologism: the origin and uses of suicide. *Suicide Life-Threatening Behav.* 24, 113–126 (1994).

9. World Health Organization. *The World Health Report 2001: Mental Health: new understanding, new hope*. (2001).

10. Baumgarten, A., Assmann, J. & Stroumsa, G. G. in *Self, Soul and Body (Studies in the history of religions 78)* 384–403 (Brill, 1998).

11. Lykouras, L., Poulakou-Rebelakou, E., Tsiamis, C. & Ploumpidis, D. Suicidal behaviour in the ancient Greek and Roman world. *Asian J. Psychiatr.* 6, 548–551 (2013).

12. Lappas, N. T. & Lappas, C. M. *Forensic Toxicology: Principles and Concepts*. *Forensic Toxicology: Principles and Concepts* (Academic Press, 2016).

13. in *Quran 4:29*

14. Cook, D. in *Islamic Studies* (Oxford University Press, 2012).

15. Karamanou, M. & Androutsos, G. in *History of toxicology and environmental health: toxicology in antiquity, volume 1* (Elsevier, 2014).

16. Lo, P.-C. in *Confucian Bioethics* (Springer, 2002).

17. Giles, H. A., Aberd, L. D. & Oxon, D. L. The Hsi Yuan Lu or Instructions to Coroners: the washing away of wrongs. *Proc R Soc Med.* 17, 59–107 (1924).

18. Aquinas, T. in *Summa Theologiae* (1485).

19. Hinduja, S. & Patchin, J. W. Bullying, cyberbullying, and suicide. *Arch. Suicide Res.* 14, 206–221 (2010).

20. World Health Organization. Global Health Observatory (GHO) data. Available at: https://www.who.int/gho/en/.

21. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 385, 117–171 (2015).

22. World Health Organization. *Preventing suicide.* 143, (2014).

23. World Health Organization. WHO Mortality Database. (2017). Available at: https://www.who.int/healthinfo/mortality_data/en/.

24. Ajdacic-Gross, V. *et al.* Methods of suicide: international suicide patterns derived from the WHO mortality database. *Bull. World Health Organ.* 86, 657–736 (2008).

25. OECD (2016), Suicide rates (indicator). Available at: https://data.oecd.org/healthstat/suicide-rates.htm.

26. Guo-Xin Jiang, Hadlaczky, G. & Wasserman, D. *NASP: Självmord i Sverige, Data: 1980-2014*. (2016).

27. Björkenstam, C., Andersson, G., Dalman, C., Cochran, S. & Kosidou, K. Suicide in married couples in Sweden: is the risk greater in same-sex couples? *Eur. J. Epidemiol.* 31, 685–690 (2016).

28. Krupinski, M. *et al.* Schizophrene psychosen und kliniksuizid: risikofaktoren, psychopharmakologische behandlung. *Nervenarzt* 71, 906–911 (2000).

29. Harris, E. C. & Barraclough, B. Suicide as an outcome for disease: a meta-analysis. *Brittish J. Psychiatry* 170, 205–228 (1997).

30. Neeleman, J. A continuum of premature death. Meta-analysis of competing mortality in the psychosocially vulnerable. *Int. J. Epidemiol.* 30, 154–62 (2001).

31. Arsenault-Lapierre, G., Kim, C. & Turecki, G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry* 4, 37 (2004).

32. Fleischmann, A., Bertolote, J. M., Belfer, M. & Beautrais, A. Completed suicide and psychiatric diagnoses in young people: a critical examination of the evidence. *Am. J. Orthopsychiatry* 75, 676–683 (2005).

33. Chesney, E., Goodwin, G. M. & Fazel, S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry* 13, 153–160 (2014).

34. Beghi, M., Rosenbaum, J. F., Cerri, C. & Cornaggia, C. M. Risk factors for fatal and nonfatal repetition of suicide attempts: A literature review. *Neuropsychiatr. Dis. Treat.* 9, 1725–1736 (2013).

35. Owens, D., Horrocks, J. & House, A. Fatal and non-fatal repetition of self-harm : systematic review. *Br. J. Psychiatry* 181, 193–199 (2002).

36. Hubers, A. A. M. *et al.* Suicidal ideation and subsequent completed suicide in both psychiatric and non-psychiatric populations: a meta-analysis. *Epidemiol. Psychiatr. Sci.* 27, 1–13 (2016).

37. Fawcett, J. *et al.* Time-related predictors of suicide in major affective disorder. *Am. J. Psychiatry* 147, 1189–1194 (1990).

38. Ludwig, B. & Dwivedi, Y. The concept of violent suicide, its underlying trait and neurobiology: a critical perspective. *Eur. Neuropsychopharmacol.* 28, 243–251 (2018).

39. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*. (American Psychiatric Publishing, 2013).

40. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.)*. (American Psychiatric Publishing, 2000).

41. World Health Organization. ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision,. (2010).

42. Hawton, K., Sutton, L., Haw, C., Sinclair, J. & Deeks, J. J. Schizophrenia and suicide: systematic review of risk factors. *Br. J. Psychiatry* 187, 9–20 (2005).

43. Chapman, C. L. *et al.* Meta-analysis of the association between suicidal ideation and later suicide among patients with either a schizophrenia spectrum psychosis or a mood disorder. *Acta Psychiatr. Scand.* 131, 162–173 (2015).

44. Oquendo, M. A., Baca-García, E., Mann, J. J. & Giner, J. Issues for DSM-V: suicidal behavior as a separate diagnosis on a separate axis. *Am. J. Psychiatry* 165, 1383–1384 (2008).

45. Blasco-Fontecilla, H. *et al.* The addictive model of self-harming (non-suicidal and suicidal) behavior. *Front. Psychiatry* 7, 1–7 (2016).

46. Razvodovsky, Y. E. Alcohol consumption and suicide trends in the former Soviet republics. *J. Psychiatry Psychiatr. Disord.* 1, 15–25 (2016).

47. Norström, T. & Rossow, I. Alcohol consumption as a risk factor for suicidal behavior: a systematic review of associations at the individual and at the population level. *Arch. suicide Res.* 20, 489–506 (2016).

48. Wilcox, H. C., Conner, K. R. & Caine, E. D. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. *Drug Alcohol Depend.* 76, 11–19 (2004).

49. Darvishi, N., Farhadi, M., Haghtalab, T. & Poorolajal, J. Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis. *PLoS One* 10, 1–14 (2015).

50. Schneider, B. Substance use disorders and risk for completed suicide. *Arch. Suicide Res.* 13, 303–316 (2009).

51. Poorolajal, J., Haghtalab, T., Farhadi, M. & Darvishi, N. Substance use disorder and risk of suicidal ideation, suicide attempt and suicide death: a meta-analysis. *J. Public Health.* 38, 282–291 (2015).

52. McGirr, A. & Turecki, G. The relationship of impulsive aggressiveness to suicidality and other depression-linked behaviors. *Curr. Psychiatry Rep.* 9, 460–466 (2007).

53. Oquendo, M. A. *et al.* Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am. J. Psychiatry* 161, 1433–1441 (2004).

54. Zouk, H., Tousignant, M., Seguin, M., Lesage, A. & Turecki, G. Characterization of impulsivity in suicide completers: clinical, behavioral and psychosocial dimensions. *J. Affect. Disord.* 92, 195–204 (2006).

55. Oquendo, M. A. *et al.* Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. *J. Affect. Disord.* 59, 107–117 (2000).

56. Impey, M. & Heun, R. Completed suicide, ideation and attempt in attention deficit hyperactivity disorder. *Acta Psychiatr. Scand.* 125, 93–102 (2012).

57. Ljung, T., Chen, Q., Lichtenstein, P. & Larsson, H. Common etiological factors of attention-deficit/hyperactivity disorder and suicidal behavior: a population-based study in Sweden. *JAMA Psychiatry* 71, 958–64 (2014).

58. Strid, J. M. C., Christiansen, C. F., Olsen, M. & Qin, P. Hospitalisation for chronic obstructive pulmonary disease and risk of suicide: a population-based case-control study. *BMJ Open* 4, 1–7 (2014).

59. Nevalainen, O. *et al.* Epilepsy, excess deaths and years of life lost from external causes. *Eur. J. Epidemiol.* 31, 445–453 (2016).

60. Bell, G. S., Gaitatzis, A., Bell, C. L., Johnson, A. L. & Sander, J. W. Suicide in people with epilepsy: how great is the risk? *Epilepsia* 50, 1933–1942 (2009).

61. Pompili, M. *et al.* Suicide risk in multiple sclerosis: a systematic review of current literature. *J. Psychosom. Res.* 73, 411–7 (2012).

62. Webb, R. T. *et al.* Suicide risk in primary care patients with major physical diseases. *Arch. Gen. Psychiatry* 69, 256–264 (2012).

63. Qin, P., Webb, R., Kapur, N. & Sørensen, H. T. Hospitalization for physical illness and risk of subsequent suicide: a population study. *J. Intern. Med.* 273, 48–58 (2013).

64. Ilgen, M. A. *et al.* Noncancer pain conditions and risk of suicide. *JAMA Psychiatry* 70, 692–697 (2013).

65. Batty, G. D., David Batty, G., Kivimaki, M., Park, I. S. & Jee, S. H. Diabetes and raised blood glucose as risk factors for future suicide: cohort study of 1 234 927 Korean men and women. *J. Epidemiol. Community Health* 66, 650–2 (2012).

66. Webb, R. T. *et al.* Unnatural deaths in a national cohort of people diagnosed with diabetes. *Diabetes Care* 37, 1–8 (2014).

67. Forsman, J. *et al.* Glucose metabolism in completed suicide : a forensic-pathological pilot study. *Croat. Med. J.* 58, 34–39 (2017).

68. Shenassa, E. D., Catlin, S. N. & Buka, S. L. Lethality of firearms relative to other suicide methods: a population based study. *J. Epidemiol. Community Health* 57, 120–124 (2003).

69. Elnour, A. A. & Harrison, J. Lethality of suicide methods. *Inj. Prev.* 14, 39–46 (2008).

70. Spicer, R. S. & Miller, T. R. Suicide acts in 8 states: Incidence and case fatality rates by demographics and method. *Am. J. Public Health* 90, 1885–1891 (2000).

71. Biddle, L. *et al.* Factors influencing the decision to use hanging as a method of suicide: qualitative study. *Br. J. Psychiatry* 197, 320–325 (2010).

72. Skopek, M. A. & Perkins, R. Deliberate exposure to motor vehicle exhaust gas: the psychosocial profile of attempted suicide. *Aust. N. Z. J. Psychiatry* 32, 830–838 (1998).

73. Eddleston, M., Karunaratne, A. & Weerakoon, M. Choice of poison for intentional self-poisoning in rural Sri Lanka. *Clin Toxicol* 44, 283–286 (2006).

74. Barber, C. W. & Miller, M. J. Means of suicide. *Am. J. Prev. Med.* 47, 264–272 (2014).

75. Gunnell, D., Middleton, N. & Frankel, S. Method availability and the prevention of suicide - a re-analysis of secular trends in England and Wales 1950-1975. *Soc. Psychiatry Psychiatr. Epidemiol.* 35, 437–443 (2000).

76. Gunnell, D. *et al.* The impact of pesticide regulations on suicide in Sri Lanka. *Int. J. Epidemiol.* 36, 1235–1242 (2007).

77. Florentine, J. B. & Crane, C. Suicide prevention by limiting access to methods: a review of theory and practice. *Soc. Sci. Med.* 70, 1626–32 (2010).

78. Reisch, T., Steffen, T., Habenstein, A. & Tschacher, W. Change in suicide rates in Switzerland before and after firearm restriction resulting from the 2003 'Army XXI' reform. *Am. J. Psychiatry* 170, 977–984 (2013).

79. Studdert, D. M., Gurrin, L. C., Jatkar, U. & Pirkis, J. Relationship between vehicle emissions laws and incidence of suicide by motor vehicle exhaust gas in Australia, 2001-06: an ecological analysis. *PLoS Med.* 7, 1–9 (2010).

80. Hawton, K. *et al.* Six-year follow-up of impact of co-proxamol withdrawal in England and Wales on prescribing and deaths: time-series study. *PLoS Med.* 9, (2012).

81. Ohberg, A., Lonnqvist, J., Sarna, S., Vuori, E. & Penttila, A. Trends and availability of suicide methods in Finland. Proposals for restrictive measures. *Br. J. Psychiatry* 166, 35–43 (1995).

82. Yip, P. S. F. *et al.* Means restriction for suicide prevention. *Lancet* 379, 2393–2399 (2012).

83. Runeson, B., Haglund, A., Lichtenstein, P. & Tidemalm, D. Suicide risk after nonfatal self-harm: a national cohort study, 2000–2008. *J. Clin. Psychiatry* 77, 240–246 (2016).

84. Pirkola, S., Sund, R., Sailas, E. & Wahlbeck, K. Community mental-health services and suicide rate in Finland: a nationwide small-area analysis. *Lancet* 373, 147–153 (2009).

85. Kawaguchi, H. & Koike, S. Association between the density of physicians and suicide rates in Japan: nationwide ecological study using a spatial Bayesian model. *PLoS One* 11, 1–9 (2016).

86. Korošec Jagodič, H., Rokavec, T., Agius, M. & Pregelj, P. Availability of mental health service providers and suicide rates in Slovenia: a nationwide ecological study. *Croat. Med. J.* 54, 444–452 (2013).

87. Kapusta, N. D. *et al.* Availability of mental health service providers and suicide rates in Austria: a nationwide study. *Psychiatr. Serv.* 61, 1198–1203 (2010).

88. Baldessarini, R. J. *et al.* Ecological studies of antidepressant treatment and suicidal risks. *Harv. Rev. Psychiatry* 15, 133–145 (2007).

89. Rajkumar, A. P., Brinda, E. M., Duba, A. S., Thangadurai, P. & Jacob, K. S. National suicide rates and mental health system indicators: an ecological study of 191 countries. *Int. J. Law Psychiatry* 36, 339–342 (2013).

90. Appleby, L., Dennehy, J. A., Thomas, C. S., Faragher, E. B. & Lewis, G. Aftercare and clinical characteristics of people with mental illness who commit suicide: a case-control study. *Lancet* 353, 1397–1400 (1999).

91. Karthick, S. & Barwa, S. A review on theoretical models of suicide. 03, 101–109 (2017).

92. Mann, J. J., Waternaux, C., Haas, G. L. & Malone, K. M. Toward a clinical model of suicidal behavior in psychiatric patients. *Am. J. Psychiatry* 156, 181–9 (1999).

93. O'Connor, R. C. & Kirtley, O. J. The integrated motivational - volitional model of suicidal behavior. *Phil. Trans. R. Soc. B* 373, (2018).

94. Maris, R. W. Suicide. *Lancet* 360, 319–326 (2002).

95. Ludwig, B., Roy, B., Wang, Q., Birur, B. & Dwivedi, Y. The life span model of suicide and its neurobiological foundation. *Front. Neurosci.* 11, 1–14 (2017).

96. Ma, J., Batterham, P. J., Calear, A. L. & Han, J. A systematic review of the predictions of the Interpersonal-Psychological Theory of Suicidal Behavior. *Clin. Psychol. Rev.* 46, 34–45 (2016).

97. Lloyd, K. G., Farley, I. J. ., Deck, J. H. N. & Homykiewicz, O. Serotonin and 5-HIAA in discrete areas of the brainstem of suicide victim patients. *Adv. Biochem. Psychopharmacol.* 11, 387–397 (1974).

98. Asberg, M., Traskman, L. & Thoren, P. 5-HIAA in the cerebrospinal fluid. *Arch. Gen. Psychiatry* 33, 1193–1197 (1976).

99. Traskman, L., Asberg, M., Bertilsson, L. & Sjostrand, L. Monoamine metabolites in CSF and suicidal behavior. *Arch. Gen. Psychiatry* 38, 631–6 (1981).

100. Banki, C. M., Arato, M., Papp, Z. & Kurcz, M. Biochemical markers in suicidal patients. Investigations with cerebrospinal fluid amine metabolites and neuroendocrine tests. *J. Affect. Disord.* 6, 341–350 (1984).

101. Mann, J., Apter, A. & Bertolote, J. Suicide prevention strategies: a systematic review. *JAMA* 294, (2005).

102. Placidi, G. P. A. *et al.* Aggressivity, suicide attempts and depression: relationship to cerebrospinal fluid monoamine metabolite levels. *Biol. Psychiatry* 50, 783–791 (2001).

103. Roy, A., Virkkunen, M., Guthrie, S. & Linnoila, M. Indices of serotonin and glucose metabolism in violent offenders, arsonists and alcoholics. *Ann. N. Y. Acad. Sci.* 487, 202–220 (1986).

104. Mann, J. J. & Currier, D. A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. *Arch. Suicide Res.* 11, 3–16 (2007).

105. Arango, V., Underwood, M. D. & Mann, J. J. Serotonin brain circuits involved in major depression and suicide. *Prog. Brain Res.* 136, 443–453 (2002).

106. Desmyter, S., Bijttebier, S. & Van Heeringen, K. The role of neuroimaging in our understanding of the suicidal brain. *CNS Neurol. Disord. - Drug Targets* 12, 921–929 (2013).

107. Culverhouse, R. C. *et al.* Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. *Mol. Psychiatry* 23, 133–142 (2018).

108. Fanelli, G. & Serretti, A. The influence of the serotonin transporter gene 5-HTTLPR polymorphism on suicidal behaviors: a meta-analysis. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 88, 375–387 (2019).

109. Turecki, G. *et al.* Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. *Am. J. Psychiatry* 156, 1456–1458 (1999).

110. Wang, J. Y. *et al.* Association of the HTR2A 102T/C polymorphism with attempted suicide: a meta-analysis. *Psychiatr. Genet.* 25, 168–177 (2015).

111. Bylund, D. B. & Reed, A. L. Childhood and adolescent depression: why do children and adults respond differently to antidepressant drugs? *Neurochem. Int.* 51, 246–253 (2007).

112. Klomp, A. *et al.* Lasting effects of chronic fluoxetine treatment on the late developing rat brain: age-dependent changes in the serotonergic neurotransmitter system assessed by pharmacological MRI. *Neuroimage* 59, 218–226 (2012).

113. Klomp, A., Václavů, L., Meerhoff, G. F., Reneman, L. & Lucassen, P. J. Effects of chronic fluoxetine treatment on neurogenesis and tryptophan hydroxylase expression in adolescent and adult rats. *PLoS One* 9, e97603 (2014).

114. Mann, J. J., Brent, D. A. & Arango, V. The neurobiology and genetics of suicide and attempted suicide: A focus on the serotonergic system. *Neuropsychopharmacology* 24, 467–477 (2001).

115. Pandey, G. N. *et al.* Platelet serotonin-2A receptors: a potential biological marker for suicidal behavior. *Am. J. Psychiatry* 152, 850–855 (1995).

116. Oquendo, M. A. *et al.* Higher postmortem prefrontal 5-HT2A receptor binding correlates with lifetime aggression in suicide. *Biol. Psychiatry* 59, 235–243 (2006).

117. Van Heeringen, K. & Mann, J. J. The neurobiology of suicide. *Lancet Psychiatry* 1, 63–72 (2014).

118. Mann, J. J. & Currier, D. M. Stress, genetics and epigenetic effects on the neurobiology of suicidal behavior and depression. *Eur. Psychiatry* 25, 268–271 (2010).

119. Pavcovich, L. A., Cancela, L. M., Volosin, M., Molina, V. A. & Ramirez, O. A. Chronic stress-induced changes in locus coeruleus neuronal activity. *Brain Res. Bull.* 24, 293–296 (1990).

120. Arango, V., Underwood, M. D. & Mann, J. J. Biologic alterations in the brainstem of suicides. *Psychiatr. Clin. North Am.* 20, 581–593 (1997).

121. Arango, V. *et al.* Autoradiographic demonstration of increased serotonin 5-HT2 and beta-adrenergic receptor binding sites in the brains of suicide victims. *Arch Gen Psychiatry* 47, 1038–1048 (1990).

122. Beskow, J., Gottfries, C. G., Roos, B. E. & Winblad, B. Determination of monoamine and monoamine metabolites in the human brain: post mortem studies in a group of suicides and in a control group. *Acta Psychiatr. Scand.* 53, 7–20 (1976).

123. Jokinen, J., Ouda, J. & Nordström, P. Noradrenergic function and HPA axis dysregulation in suicidal behaviour. *Psychoneuroendocrinology* 35, 1536–1542 (2010).

124. Traskman-Bendz, L. Prediction of suicidal behavior from biological tests. *J. Clin. Psychopharmacol.* 12, S21–S27 (1992).

125. Stetler, C. & Miller, G. E. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosom. Med.* 73, 114–126 (2011).

126. RC, M., Nestler, E. & Hyman, S. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*. (McGraw-Hill, 2009).

127. Fischer, S., Strawbridge, R., Herane Vives, A. & Cleare, A. J. Cortisol as a predictor of psychological therapy response in depressive disorders: systematic review and meta-analysis. *Br. J. Psychiatry* (2016).

128. Kessing, L. V., Willer, I. S. & Knorr, U. Volume of the adrenal and pituitary glands in depression. *Psychoneuroendocrinology* 36, 19–27 (2011).

129. Szigethy, E., Conwell, Y., Forbes, N. T., Cox, C. & Caine, E. D. Adrenal weight and morphology in victims of completed suicide. *Biol. Psychiatry* 36, 374–380 (1994).

130. Arató, M., Bánki, C. M., Bissette, G. & Nemeroff, C. B. Elevated CSF CRF in suicide victims. *Biol. Psychiatry* 25, 355–359 (1989).

131. Nemeroff, C. B., Owens, M. J., Bissette, G., Andorn, A. C. & Stanley, M. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Arch. Gen. Psychiatry* 45, 577–579 (1988).

132. Tidemalm, D. *et al.* Familial clustering of suicide risk: a total population study of 11.4 million individuals. *Psychol. Med.* 41, 2527–2534 (2011).

133. Brent, D. A. & Melhem, N. Familial transmission of suicidal behavior. *Psychiatr. Clin. North Am.* 31, 157–177 (2008).

134. Galfalvy, H. *et al.* A pilot genome-wide association and gene expression array study of suicide with and without major depression. *World J. Biol. Psychiatry* 14, 574–582 (2013).

135. Galfalvy, H. *et al.* A genome-wide association study of suicidal behavior. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 168, 557–563 (2015).

136. Robins, E., Gassner, S., Kayes, J., Wilkinson, R. H. & Murphy, G. E. The communication of suicidal intent: a study of 134 consecutive cases of successful (completed) suicide. *Am. J. Psychiatry* 115, 724–733 (1959).

137. Isometsä, E. T. Psychological autopsy studies – a review. *Eur. Psychiatry* 16, 379–385 (2001).

138. Zhou, X. M. & Jia, S. H. Suicidal communication signifies suicidal intent in Chinese completed suicides. *Soc. Psychiatry Psychiatr. Epidemiol.* 47, 1845–1854 (2012).

139. Luoma, J. B., Martin, C. E. & Pearson, J. L. Contact with mental health and primary care providers before suicide : a review of the evidence. *Am. J. Psychiatry* 159, 909–916 (2002).

140. Ahmedani, B. K. *et al.* Health care contacts in the year before suicide death. *J. Gen. Intern. Med.* 29, 870–877 (2014).

141. Large, M., Ryan, C. & Nielssen, O. The validity and utility of risk assessment for inpatient suicide. *Australas. Psychiatry* 19, 507–12 (2011).

142. Riley, R. D. Commentary: Like it and lump it? Meta-analysis using individual participant data. *Int. J. Epidemiol.* 39, 1359–1361 (2010).

143. Giner, L. *et al.* Personality disorders and health problems distinguish suicide attempters from completers in a direct comparison. *J. Affect. Disord.* 151, 474–483 (2013).

144. Klonsky, E. D., May, A. M. & Saffer, B. Y. Suicide, suicide attempts, and suicidal ideation. *Annu. Rev. Clin. Psychol.* 12, 307–330 (2016).

145. Swedish Council on Health Technology Assessment (SBU). *Instruments for suicide risk assessment*. (2015).

146. Fazel, S. & Wolf, A. Suicide risk assessment tools do not perform worse than clinical judgement. *Br. J. Psychiatry* 211, 183 (2017).

147. Roos, L., Sareen, J. & Bolton, J. M. Suicide risk assessment tools, predictive validity findings and utility today: time for a revamp? *Neuropsychiatry (London).* 3, 1–13 (2013).

148. World Health Organization. *Introduction to Drug Utilization Research*. (2003).

149. Thomas, K. H., Martin, R. M., Potokar, J., Pirmohamed, M. & Gunnell, D. Reporting of drug induced depression and fatal and non-fatal suicidal behaviour in the UK from 1998 to 2011. *BMC Pharmacol. Toxicol.* 15, 54 (2014).

150. Brooks, J. M. & Ohsfeldt, R. L. Squeezing the balloon: propensity scores and unmeasured covariate balance. *Health Serv. Res.* 48, 1487–1507 (2013).

151. Isacsson, G., Rich, C. L., Jureidini, J. & Raven, M. The increased use of antidepressants has contributed to the worldwide reduction in suicide rates. *Br. J. Psychiatry* 196, 429–433 (2010).

152. Beasley, C. M. *et al.* Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 303, 685–92 (1991).

153. Tec, L. The treatment of enuresis with imipramine. *Am. J. Psychiatry* 125, 162 (1968).

154. Damlujim, N. F. & Ferguson, J. M. Paradoxical worsening of depressive symptomatology caused by antidepressants. *J. Clin. Psychopharmacol.* 8, 347–349 (1988).

155. King, R. A. *et al.* Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. *J. Am. Acad. child Adolesc. psychiatry* 30, 179–186 (1991).

156. Teicher, M. H., Glod, C. & Cole, J. O. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am. J. Psychiatry* 147, 207–210 (1990).

157. Khan, A., Warner, H. A. & Brown, W. A. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. *Arch. Gen. Psychiatry* 57, 311–317 (2000).

158. Storosum, J. G., van Zwieten, B. J., van den Brink, W., Gersons, B. P. R. & Broekmans, A. W. Suicide risk in placebo-controlled studies of major depression. *Am. J. Psychiatry* 158, 1271–1275 (2001).

159. Isacsson, G. Suicide prevention - a medical breakthrough? *Acta Psychiatr. Scand.* 102, 113–117 (2000).

160. Grunebaum, M. F., Ellis, S. P., Li, S., Oquendo, M. A. & Mann, J. J. Antidepressants and suicide risk in the United States, 1985-1999. *J. Clin. Psychiatry* 65, 1456–1462 (2004).

161. Ernst, C. L. & Goldberg, J. F. Antisuicide properties of psychotropic drugs: a critical review. *Harv. Rev. Psychiatry* 12, 14–41 (2004).

162. Corrado, B., Eleonora, E. & Cipriani, A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *CMAJ* 180, 291–297 (2009).

163. Rubino, A. *et al.* Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study. *BMJ* 334, 242 (2007).

164. Cheung, K. *et al.* Antidepressant use and the risk of suicide: a population-based cohort study. *J. Affect. Disord.* 174, 479–484 (2015).

165. Schneeweiss, S. *et al.* Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults. *Arch. Gen. Psychiatry* 67, 497 (2010).

166. Rahme, E., Dasgupta, K., Turecki, G., Nedjar, H. & Galbaud du Fort, G. Risks of suicide and poisoning among elderly patients prescribed selective serotonin reuptake inhibitors: a retrospective cohort study. *J. Clin. Psychiatry* 69, 349–57 (2008).

167. Tiihonen, J. *et al.* Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Arch. Gen. Psychiatry* 63, 1358–1367 (2006).

168. Yerevanian, B. I., Koek, R. J., Feusner, J. D., Hwang, S. & Mintz, J. Antidepressants and suicidal behaviour in unipolar depression. *Acta Psychiatr. Scand.* 110, 452–458 (2004).

169. Khan, A., Fahl Mar, K., Gokul, S. & Brown, W. A. Decreased suicide rates in recent antidepressant clinical trials. *Psychopharmacology.* 235, 1455–1462 (2018).

170. Juurlink, D. N. *et al.* The risk of suicide with selective serotonin reuptake inhibitors in the elderly. *Am J Psychiatry* 163, 813–821 (2006).

171. Hammad, Tarek A, Laugren Thomas, R. J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch. Gen. Psychiatry* 63, 332–339 (2006).

172. Olfson, M., Marcus, S. C. & Shaffer, D. A. Antidepressant drug therapy and suicide in severely depressed children and adults: a case-control study. *Arch Gen Psychiatry* 63, 865–872 (2006).

173. Lu, C. Y. *et al.* Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. *BMJ* 348, (2014).

174. Hetrick, S., McKenzie, J., Cox, G., Simmons, M. & Merry, S. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst. Rev.* 11, (2012).

175. Cooper, W. O. *et al.* Antidepressants and suicide attempts in children. *Pediatrics* 133, 204–10 (2014).

176. Miller, M. *et al.* Antidepressant class, age, and the risk of deliberate self-harm: a propensity score matched cohort study of SSRI and SNRI users in the USA. *CNS Drugs* 28, 79–88 (2014).

177. Valuck, R. J., Libby, A. M., Sills, M. R., Giese, A. A. & Allen, R. R. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS Drugs* 18, 1119–32 (2004).

178. Christiansen, E., Agerbo, E., Bilenberg, N. & Stenager, E. SSRIs and risk of suicide attempts in young people – a Danish observational register-based historical cohort study, using propensity score. *Nord. J. Psychiatry* 70, 167–175 (2016).

179. Fazel, S., Wolf, A., Palm, C. & Lichtenstein, P. Violent crime, suicide, and premature mortality in patients with schizophrenia and related disorders: a 38-year total population study in Sweden. *Lancet Psychiatry* 1, 44–54 (2014).

180. Popovic, D. *et al.* Risk factors for suicide in schizophrenia: systematic review and clinical recommendations. *Acta Psychiatr. Scand.* 130, 418–426 (2014).

181. Cassidy, R. M., Yang, F., Kapczinski, F. & Passos, I. C. Risk factors for suicidality in patients with schizophrenia : a systematic review, meta-analysis, and meta-regression of 96 studies. *Schizophr. Bull.* 44, 787–797 (2018).

182. Yates, K. *et al.* Association of psychotic experiences with subsequent risk of suicidal ideation, suicide attempts, and suicide deaths: a systematic review and meta-analysis of longitudinal population studies. *JAMA Psychiatry* 1–10 (2018).

183. Minzenberg, M. J. *et al.* Frontal cortex control dysfunction related to long-term suicide risk in recent-onset schizophrenia. *Schizophr. Res.* 157, 19–25 (2014).

184. Meltzer, H. Y. in *Neuropsychopharmacology – 5th Generation of Progress* (American College of Neuropsychopharmacology, 2002).

185. Hennen, J. & Baldessarini, R. J. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophr. Res.* 73, 139–145 (2005).

186. Tiihonen, J. *et al.* 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 374, 620–627 (2009).

187. Haukka, J., Tiihonen, J., Harkanen, T. & Lönnqvist, J. Association between medication and risk of suicide, attempted suicide and death in nationwide cohor of suicidal patients with schizophrenia. *Pharmacoepidemiol. Drug Saf.* 17, 686–696 (2008).

188. Ringback Weitoft, G. *et al.* Mortality, attempted suicide, re-hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden—a register-based study. *Pharmacoepidemiol. Drug Saf.* 23, 290–298 (2014).

189. Vermeulen, J. M. *et al.* Clozapine and Long-Term Mortality Risk in Patients With Schizophrenia: A Systematic Review and Meta-analysis of Studies Lasting 1.1–12.5 Years. *Schizophr. Bull.* 1–15 (2018). doi:10.1093/schbul/sby052

190. Meltzer, H. Y. *et al.* Clozapine treatment for suicidality in schizophrenia. *Arch. Gen. Psychiatry* 60, 82–91 (2003).

191. Yerevanian, B. I., Koek, R. J. & Mintz, J. Bipolar pharmacotherapy and suicidal behavior. Part 3: Impact of antipsychotics. *J. Affect. Disord.* 103, 23–28 (2007).

192. Brotman, M. A., Fergus, E. L., Post, R. M. & Leverich, G. S. High exposure to neuroleptics in bipolar patients: a retrospective review. *J. Clin. Psychiatry* 67–74 (2000).

193. Seemüller, F. *et al.* Akathisia and suicidal ideation in first-episode schizophrenia. *J. Clin. Psychopharmacol.* 32, 694–8 (2012).

194. Schneider-Thoma, J. *et al.* Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomised controlled trials. *Lancet Psychiatry* 5, 653–663 (2018).

195. Tiihonen, J., Mittendorfer-Rutz, E., Torniainen, M., Alexanderson, K. & Tanskanen, A. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. *Am. J. Psychiatry* 173, 600–606 (2016).

196. Torniainen, M. *et al.* Antipsychotic treatment and mortality in schizophrenia. *Schizophr. Bull.* 41, 656–663 (2015).

197. Pompili, M. *et al.* Do atypical antipsychotics have antisuicidal effects? a hypothesis-generating overview. *Int. J. Mol. Sci.* 17, (2016).

198. Kiviniemi, M. *et al.* Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. *Schizophr. Res.* 150, 274–280 (2013).

199. Neuner, T. *et al.* Completed suicides in 47 psychiatric hospitals in Germany results from the AGATE-study. *Pharmacopsychiatry* 44, 324–330 (2011).

200. Hielä, H. *et al.* Suicide victims with schizophrenia in different treatment phases and adequacy of antipsychotic medication. *J Clin Psychiatry* 60, 200–208 (1999).

201. Taiminen, T. J. & Kujari, H. Antipsychotic medication and suicide risk among schizophrenia and paranoid inpatients. A controlled retrospective study. *Acta Psychiatr Scand* 90, 247–251 (1994).

202. Cheng, K. K., Leung, C. M., Lo, W. H. & Lam, T. H. Risk factors of suicide among schizophrenics. *Acta Psychiatr. Scand.* 81, 220–224 (1990).

203. Palmer, D. D., Henter, I. D. & Wyatt, R. J. Do antipsychotic medications decrease the risk of suicide in patients with schizophrenia? *J. Clin. Psychiatry* 60, 100–103 (1999).

204. Khan, A., Khan, S. R., Leventhal, R. M. & Brown, W. A. Symptom reduction and suicide risk in patients treated with placebo in antipsychotic clinical trials: an analysis of the Food and Drug Administration database. *Am. J. Psychiatry* 158, 1449–1454 (2001).

205. Karayal, O. N., Anway, S. D., Batzar, E. & Vanderburg, D. G. Assessments of suicidality in double-blind, placebo-controlled trials of ziprasidone. *J. Clin. Psychiatry* 72, 367–375 (2011).

206. Lewitzka, U., Severus, E., Bauer, R., Ritter, P. & Bauer, M. The suicide prevention effect of lithium : more than 20 years of evidence — a narrative review. *Int. J. Bipolar Disord.* (2015).

207. Cipriani, A., Hawton, K., Stockton, S. & Geddes, J. R. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 3646, 1–13 (2013).

208. Gonzalez-Pinto, A. *et al.* Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord.* 8, 618–624 (2006).

209. World Health Organization. *Adherence to long-term therapies: evidence for action*. (2003).

210. Mibei, F. Non-compliance to medication in psychiatric patients: a literature review. (Turku University, 2013).

211. Colom, F. & Vieta, E. Non-adherence in psychiatric disorders: misbehaviour or clinical feature? *Acta Psychiatr. Scand.* 105, 161–163 (2002).

212. Sites, B. D., Masaracchia, M. M. & Davis, M. Distinguishing between efficacy and real-world effectiveness. *Reg. Anesth. Pain Med.* 42, 131–132 (2017).

213. Carow, F. *et al.* Objective assessment of nonadherence and unknown co-medication in hospitalized patients. *Eur. J. Clin. Pharmacol.* 68, 1191–1199 (2012).

214. Coughlin, S. S. Recall bias in epidemiologic studies. *J. Clin. Epidemiol.* 43, 87–91 (1990).

215. Modi, A. C., Ingerski, L. M., Rausch, J. R., Glauser, T. A. & Drotar, D. White-coat adherence over the first year of therapy in pediatric epilepsy. *J. Pediatr.* 161, 695–699 (2012).

216. de Jager, R. L., van Maarseveen, E. M., Bots, M. L. & Blankestijn, P. J. Medication adherence in patients with apparent resistant hypertension: findings from the SYMPATHY trial. *Br. J. Clin. Pharmacol.* (2017).

217. Martin-Facklam, M. *et al.* Undeclared exposure to St. John's wort in hospitalized patients. *Br. J. Clin. Pharmacol.* 58, 437–441 (2004).

218. Loayza, N., Crettol, S., Riquier, F. & Eap, C. B. Adherence to antidepressant treatment: what the doctor thinks and what the patient says. *Pharmacopsychiatry* 45, 204–207 (2012).

219. Roberson, A. M., Castro, V. M., Cagan, A. & Perlis, R. H. Antidepressant nonadherence in routine clinical settings determined from discarded blood samples. *J. Clin. Psychiatry* 77, 359–362 (2016).

220. Andrade, S. E., Kahler, K. H., Frech, F. & Chan, K. A. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol. Drug Saf.* 15, 565–574 (2006).

221. Nielsen, Lars Hougaard; Lokkegaard, Ellen; Andreasen, Anne Helms; Keiding, N. Using prescription registries to define continuous drug use: how to fill gaps between prescriptionsy. *Pharmacoepidemiol. Drug Saf.* 17, 384–388 (2008).

222. Wijk, B. L. G. Van, Klungel, O. H., Heerdink, E. R. & Boer, A. De. Refill persistence with chronic medication assessed from a pharmacy database was influenced by method of calculation. 59, 11–17 (2006).

223. Wijlaars, L. P. M. M., Nazareth, I., Whitaker, H. J., Evans, S. J. W. & Petersen, I. Suicide-related events in young people following prescription of SSRIs and other antidepressants: a self-controlled case series analysis. *BMJ Open* 3, e003247 (2013).

224. Ward, A., Ishak, K., Proskorovsky, I. & Caro, J. Compliance with refilling prescriptions for atypical antipsychotic agents and its association with the risks for hospitalization, suicide, and death in patients with schizophrenia in Quebec and Saskatchewan: a retrospective database study. *Clin. Ther.* 28, 1912–1921 (2006).

225. Tanskanen, A. *et al.* From prescriptions to drug use periods - a second generation method (PRE2DUP). *BMC Res. Notes* 15, 1–13 (2015).

226. Taipale, H. *et al.* Antipsychotic doses among community-dwelling persons with Alzheimer disease in Finland. *J. Clin. Psychopharmacol.* 34, 435–40 (2014).

227. Taipale, H. *et al.* Antidementia drug use among community-dwelling individuals with Alzheimer's disease in Finland: a nationwide register-based study. *Int. Clin. Psychopharmacol. 2014* 29, 216–223 (2014).

228. Taipale, H. *et al.* Antipsychotic polypharmacy among a nationwide sample of community-dwelling persons with Alzheimer's disease. *J. Alzheimer's Dis.* 41, 1223–1228 (2014).

229. Taipale, H. *et al.* Agreement between PRE2DUP register data modeling method and comprehensive drug use interview among older persons. *Clin. Epidemiol.* 8, 363–371 (2016).

230. National Center for Health Statistics. NCHS Data on Drug-poisoning Deaths. (2016). Available at: https://www.cdc.gov/nchs/data/factsheets/factsheet-drug-poisoning.htm.

231. Gruszecki, A. C., Booth, J. & Davis, G. G. The predictive value of history and scene investigation for toxicology results in a medical examiner population. *Am. J. Forensic Med. Pathol.* 28, 103–6 (2007).

232. Roman, M., Strom, L., Tell, H. & Josefsson, M. Liquid chromatography/time-of-flight mass spectrometry analysis of postmortem blood samples for targeted toxicological screening. *Anal. Bioanal. Chem.* 405, 4107–4125 (2013).

233. Linnet, K. Toxicological screening and quantitation using liquid chromatography/time-of-flight mass spectrometry. *J. Forensic Sci. Criminol.* 1, 9–10 (2013).

234. Darke, S., Duflou, J. & Torok, M. Drugs and violent death: comparative toxicology of homicide and non-substance toxicity suicide victims. *Addiction* 104, 1000–1005 (2009).

235. Karch, D. L., Barker, L. & Strine, T. W. Race/ethnicity, substance abuse, and mental illness among suicide victims in 13 US states: 2004 data from the National Violent Death Reporting System. *Inj. Prev.* 12, ii22-ii27 (2006).

236. Drasch, G., Dahlmann, F., Meyer, L. Von & Roider, G. Frequency of different anti-depressants associated with suicides and drug deaths. *Int. J. Legal Med.* 122, 115–121 (2008).

237. Connor, S. M., Richard, R. G., George, W. I. W. & Jason, B. D. Gender differences in the presence of drugs in violent deaths. *Addiction* 108, 547–555 (2013).

238. Sheehan, C. M., Rogers, R. G. & Boardman, J. D. Postmortem presence of drugs and method of violent suicide. *J. Drug Issues* 45, 249–262 (2015).

239. Fanton, L. *et al.* Toxicologic aspects of deaths due to falls from height. *Am. J. Forensic Med. Pathol.* 28, 262–266 (2007).

240. Frey, R. *et al.* Suicide by antidepressant intoxication identified at autopsy in Vienna from 1991-1997: the favourable consequences of the increasing use of SSRIs. *Eur. Neuropsychopharmacol.* 10, 133–142 (2000).

241. Dhossche, D. M. Toxicology of suicide: touchstone for suicide prevention? *Med. Sci. Monit.* 9, SR9-SR19 (2003).

242. Pelissier-Alicot, A.-L., Gaulier, J.-M., Champsaur, P. & Marquet, P. Mechanisms underlying postmortem redistribution of drugs: a review. *J. Anal. Toxicol.* 27, 533–544 (2003).

243. Cook, D. S., Braithwaite, R. A. & Hale, K. A. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. *J Clin Pathol* 53, 282–285 (2000).

244. Launiainen, T. & Ojanperä, I. Drug concentrations in post-mortem femoral blood compared with therapeutic concentrations in plasma. *Drug Test. Anal.* 308–316 (2013).

245. Linnet, K. Postmortem drug concentration intervals for the non-intoxicated state - a review. *J. Forensic Leg. Med.* 19, 245–249 (2012).

246. Gerostamoulos, D. *et al.* The effect of the postmortem interval on the redistribution of drugs: a comparison of mortuary admission and autopsy blood specimens. *Forensic Sci. Med. Pathol.* 8, 373–379 (2012).

247. Zilg, B., Thelander, G., Giebe, B. & Druid, H. Postmortem blood sampling—comparison of drug concentrations at different sample sites. *Forensic Sci. Int.* 278, 296–303 (2017).

248. Vieweg, W. V. R. *et al.* Child and adolescent suicides in Virginia: 1987 to 2003. *J. Child Adolesc. Psychopharmacol.* 15, 655–663 (2005).

249. Hoiseth, G., Bramness, J. G., Christophersen, A. S. & Morland, J. Carisoprodol intoxications: a retrospective study of forensic autopsy material from 1992–2003. *Int. J. Legal Med.* 121, 403–409 (2007).

250. Carson, H. J. Classes of drugs and their prevalence in multiple drug intoxication in suicides and accidents. *Leg. Med.* 10, 92–95 (2008).

251. Lin, P. T. & Gill, J. R. Subway train-related fatalities in New York City: accident versus suicide. *J. Forensic Sci.* 54, 1414–8 (2009).

252. Henriksson, S., Boethius, G. & Isacsson, G. Suicides are seldom prescribed antidepressants: findings from a prospective prescription database in Jamtland county, Sweden, 1985-95. *Acta Psychiatr. Scand.* 103, 301–306 (2001).

253. Malmvik, J., Lowenhielm, C. G. & Melander, A. Antidepressants in suicide: differences in fatality and drug utilisation. *Eur J Clin Pharmacol* 46, 291–294 (1994).

254. Isacsson, G., Bergman, U. & Rich, C. L. Antidepressants, depression and suicide: an analysis of the San Diego study. *Journal of Affective Disorders* 32, 277–286 (1994).

255. Isacsson, G., Holmgren, P. & Ahlner, J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: A controlled forensic database study of 14 857 suicides. *Acta Psychiatr. Scand.* 111, 286–290 (2005).

256. Isacsson, G. & Ahlner, J. Antidepressants and the risk of suicide in young persons – prescription trends and toxicological analyses. *Acta Psychiatr. Scand.* 129, 296–302 (2014).

257. Benson, T., Corry, C., O'Neill, S., Murphy, S. & Bunting, B. Use of prescription medication by individuals who died by suicide in Northern Ireland. *Arch. Suicide Res.* 1, 139–152 (2018).

258. Ludvigsson, J. F., Otterblad-Olausson, P., Pettersson, B. U. & Ekbom, A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur. J. Epidemiol.* 24, 659–667 (2009).

259. Brooke, H. L. *et al.* The Swedish cause of death register. *Eur. J. Epidemiol.* 32, 765–773 (2017).

260. Wettermark, B. *et al.* The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol. Drug Saf.* 16, 726–735 (2007).

261. Ludvigsson, J. F. *et al.* External review and validation of the Swedish national inpatient register. *BMC Public Health* 11, (2011).

262. Ludvigsson, J. F. *et al.* Registers of the Swedish total population and their use in medical research. *Eur. J. Epidemiol.* 31, 125–136 (2016).

263. Druid, H. & Holmgren, P. A compilation of fatal and control concentrations of drugs in postmortem femoral blood. *J. Forensic Sci.* 42, 79–87 (1997).

264. Rothman, K. J. *Epidemiology: An Introduction*. (Oxford University Press, 2012).

265. Fazel, S., Grann, M., Ahlner, J. & Goodwin, G. Suicides by violent means in individuals taking SSRIs and other antidepressants: a postmortem study in Sweden, 1992-2004. *J. Clin. Psychopharmacol.* 27, 503–6 (2007).

266. Molero, Y., Lichtenstein, P., Zetterqvist, J., Gumpert, C. H. & Fazel, S. Selective serotonin reuptake inhibitors and violent crime: a cohort study. *PLOS Med.* 12, e1001875 (2015).

267. Hemminki, E. *et al.* Antidepressant use and violent crimes among young people: a longitudinal examination of the Finnish 1987 birth cohort. *J. Epidemiol. Community Health* 71, 12–18 (2016).

268. Rahikainen, A. L., Majaharju, S., Haukka, J., Palo, J. U. & Sajantila, A. Serotonergic 5HTTLPR/rs25531 s-allele homozygosity associates with violent suicides in male citalopram users. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 174, 691–700 (2017).

269. Calati, R. *et al.* Antidepressants in elderly: metaregression of double-blind, randomized clinical trials. *J. Affect. Disord.* 147, 1–8 (2013).

270. Peñas-Lledó, E. *et al.* ABCB1 gene polymorphisms and violent suicide attempt among survivors. *J. Psychiatr. Res.* 61, 52–56 (2015).

271. Moreno, S. B. *et al.* ABCB1 gene polymorphisms are associated with suicide in forensic autopsies. *Pharmacogenet. Genomics* 23, 463–469 (2013).

272. Cramer, J. & Rosenheck, R. Compliance with medication in psychiatry and physical disorder. *Psychiatr. Serv.* 49, 196–201 (1998).

273. Bulloch, A. G. M. & Patten, S. B. Non-adherence with psychotropic medications in the general population. *Soc. Psychiatry Psychiatr. Epidemiol.* 45, 47–56 (2010).

274. Geretsegger, C. *et al.* Non-adherence to psychotropic medication assessed by plasma levels in newly admitted psychiatric patients. *Psychiatry Clin. Neurosci.* (2018).

275. Hedna, K. *et al.* Antidepressants and suicidal behaviour in late life: a prospective population-based study of use patterns in new users aged 75 and above. *Eur. J. Clin. Pharmacol.* 201–208 (2017).

276. Pettersson, G. & Eriksson, A. Unnatural deaths must be investigated better –risk of crimes being missed: examination of the police and the health care system management of deaths in three counties. *Lakartidningen* 111, 2160–2 (2014).

277. Rockett, I. R. H. *et al.* Discerning suicide in drug intoxication deaths: Paucity and primacy of suicide notes and psychiatric history. *PLoS One* 13, 1–13 (2018).

278. Salas, M., Hofman, A. & Strieker, H. C. B. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am. J. Epidemiol.* 149, 981–983 (1997).

279. Ojanperä, I., Kriikku, P. & Vuori, E. Fatal toxicity index of medicinal drugs based on a comprehensive toxicology database. *Int. J. Legal Med.* 130, 1209–1216 (2016).

13 OTHER RELATED PUBLICATIONS

During the course of the doctoral project the following publications related to the main topic and methodologies have also been published.

Jonatan Hedlund, **Jonas Forsman**, Joakim Sturup, Thomas Masterman. Pre-offense alcohol intake in homicide offenders and victims: a forensic-toxicological case-control study. *J. Forensic Leg. Med.* 56, 55–58 (2018).

Jonatan Hedlund, **Jonas Forsman**, Joakim Sturup, Thomas Masterman. Psychotropic medications in Swedish homicide victims and offenders: a forensic-toxicological case-control study of adherence and recreational use. *J. Clin. Psychiatry* 78, 797–802 (2017).

Jonas Forsman, Terhi Keltanen, Benny Liberg, Antti Sajantila, Thomas Masterman, Katarina Lindroos. Glucose metabolism in completed suicide: a forensic-pathological pilot study. *Croat Med. J* 58**,** 34–39 (2017).

Konstantinos Fountoulakis, Isaia Chatzikosta, Pastiadis Konstantinos … **Jonas Forsman,** et al. Relationship of suicide rates with climate and economic variables in Europe during 2000-2012. *Ann. Gen. Psychiatry* 15, 1–6 (2016).

Fountoulakis Konstantinos, Wolfram Kawohl, Pavlos Theodorakis… **Jonas Forsman.,** et al. Relationship of suicide rates to economic variables in Europe: 2000-2011. *Br. J. Psychiatry* 205**,** 486-496–2011 (2014).